BENZOTRIAZOLE-MEDIATED SYNTHESES OF HETEROCYCLES

BY

CLARA NANFE FALI

A DISSERTATION PRESENTED TO THE GRADUATE SCHOOL OF THE UNIVERSITY OF FLORIDA IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE OF DOCTOR OF PHILOSOPHY

UNIVERSITY OF FLORIDA

1997

To my husband Dama and children Hyallayar, Nirhyal and Hyalnga.

ACKNOWLEDGEMENTS

I would like to thank my supervisor Professor Alan R. Katritzky for his guidance and support over the years. I would also like to express my sincere gratitude to my supervisory committee members Dr. William R. Dolbier, Dr. Martin Vala, Dr. Nicholas S. Bodor and Dr. James A. Deyrup, for their assistance and suggestions.

I would like to express my special thanks to Dr. Junqing Li for his help and useful suggestions during the last two years, and Dr. Daniela Onicu and Dr. Ming Qi for their useful suggestions and assistance with part of this work. I am very grateful to all members of the ARK group and to my friends for their friendship and support.

I am particularly indebted to my parents for their encouragement and to my husband and children for their love, patience and support.

Finally I would like to thank God for seeing me through this program.

TABLE OF CONTENTS

Abstract of Dissertation Presented to the Graduate School of the University of Florida in Partial Fulfillment of the Requirements for the Degree of Doctor of Philosophy

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By

Clara Nanfe Fah

December 1997

Chairman Alan R Katritzky
Major Department Chemistry

2 [(Benzotriazol-1-yl)methyl]-pyrroles and -indoles were prepared and converted into the corresponding fused [1,2-*a*]pyrroles and fused [1,2-*a*]indoles by intramolecular cyclizations involving [3+2] and [3+3] annulations respectively The benzotriazolyl-CH-ring moieties of these derivatives were further elaborated by i) acylation and subsequent reduction and elimination promoted by $LiAlH_4$, ii) nucleophilic displacement of the benzotriazolyl moiety with NaCN, NaSPh and Grignard reagents, iii) base-assisted eliminations of benzotriazole, iv) reaction with an α,β unsaturated ketone or aldehyde followed by acid assisted elimination of the benzotriazolyl group, and v) Lewis acid promoted dimerization

2-(Benzotriazol-1-ylmethyl)furans, prepared from 1-propargylbenzotriazole, underwent 1,4 addition reactions with various α,β-unsaturated ketones and aldehydes. Intramolecular cyclization of the 1,4 products in the presence of acids gave various substituted benzo[*b*]furans. The reaction of *ortho*-iodophenol with

1 propargylbenzotriazole in the presence of $(PPh_3)_2PdCl_2$, CuI, and Et_3N gave 2-(benzotriazol-1-ylmethyl)benzo[*b*]furan The presence of the benzotriazolyl group allowed further elaboration of the $-CH_2$ side chain by i) 1,4-addition to *trans*-cinnamaldehyde, followed by intramolecular cyclization, ii) alkylation with benzyl bromide followed by elimination or nucleophilic displacement of the benzotriazolyl moiety with Grignard reagent, iii) alkylation with $(CH_3)_3CCHO$ followed by low-valent titanium promoted olefination, and iv) alkylation with benzaldehyde followed by Lewis acid catalyzed pinacol type reaction.

1-(Azidomethyl)benzotriazole reacted with alkynes to give mixtures of isomeric 1,2,3-triazoles, whereas the reactions of 1-(azidomethyl)-benzotriazole and 5 phenyl -1,2,3,4-tetrazole with alkenes proceeded regioselectively to form 1,2,3-triazolines and/or aziridines and enamines in good yields. The diheterocyclo-substituted methanes thus obtained were investigated with respect to thermolysis, α lithiation, and reactions with Grignard reagents.

1-Dialkylaminomethylbenzotriazoles reacted with ethyl propiolate and dimethyl acetylenedicarboxylate by addition of the benzotriazole anion followed by the immonium cation The benzotriazolyl group in the products underwent facile nucleophilic displacement

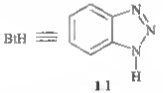
(Benzotriazol-1 yl)carbonyl chloride, generated from benzotriazole and phosgene, was reacted with *t*-butyl alcohol and *p*-methoxybenzyl alcohol to give 1-(*t* butoxycarbonyl)benzotriazole and 1-(*p*-methoxy benzyloxycarbonyl)benzotriazole, respectively, in good yields The synthetic utility of these reagents was demonstrated by effective amino protection of phenylalanine and phenylglycine

Allyllithiums were generated by the reaction of α-substituted allylbenzotriazoles with an excess of lithium. The allyllithiums thus generated were trapped readily with aldehydes and ketones with high regioselectivity and good yields. When the method was applied to γ-substituted allylbenzotriazole, similar results were observed.

CHAPTER I
GENERAL INTRODUCTION

The use of benzotriazole **1 1** as a synthetic auxiliary in the preparation of many useful organic compounds has been widely investigated by Katritzky and co-workers [91T2683, 94S445; 97CRip] Due to its good leaving ability, a benzotriazole substituent can be used in place of halogens in many reactions. The advantage of the benzotriazolyl group lies in the fact that its derivatives are often more stable and easy to handle than their chloro or bromo analogues In addition, benzotriazole is stable and inexpensive The objective of the work described in this dissertation is to further explore the use of benzotriazole as a synthetic auxiliary in the synthesis of a variety of heterocycles

As a synthetic auxiliary, the benzotriazole group has the following properties i) it can easily be introduced into a substrate either by substitution or addition reactions [87JCS(P1)791, 91T2683, 94JMC2754 97CRip],



1 1

Figure 1 1

ii) Due to its electron withdrawing properties, the benzotriazole group can activate an α-hydrogen towards proton loss (**1 3**), and it can stabilize the carbanion thus formed

In this respect, the benzotriazole is comparable to a cyano group and better than either a phenyl or a vinyl group [94S445, 91T2683, 97CRip]

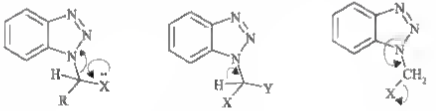


Figure 1.2

iii) Benzotriazole possesses both electron donating (**1.4**) and electron withdrawing properties (**1.2**) and as a result, compounds with an α hetero atom attached to the benzotriazole nitrogen can ionize either to **1.5** or **1.7** as shown in figure 1.3

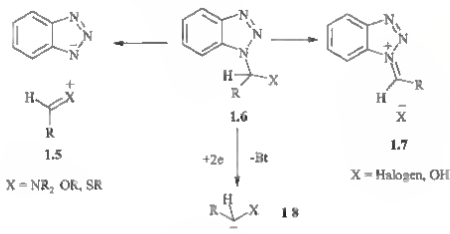


Figure 1.3

When activated by electron donor atoms (**1.2**), benzotriazole can act as a good leaving group and can be displaced by a variety of nucleophiles at the end of a synthetic transformation by trapping **1.5** with nucleophiles or hydrolysis, by ring scission of **1.6** or trapping **1.8** with electrophiles.

The combination of benzotriazole and propargyl moieties generates an interesting precursor (**1.9**) which can undergo a variety of synthetic transformations.

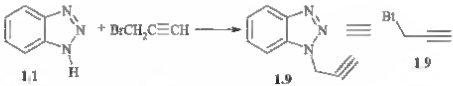
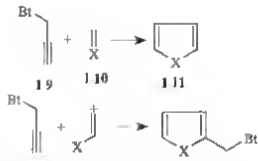


Figure 1.4

The preparation of 1-propargylbenzotriazole (**1.9**) and some regioselective reactions of its mono and dianions with electrophiles have been studied by Katritzky and co-workers [92LA843]. The addition of electrophile can be directed to occur either at the sp- or sp^3-hybridized carbon or at both centers [92LA843]. Various heterocycles have been synthesized in which 1-propargylbenzotriazole served as a three- or two- carbon unit in a [3+2] annulation as illustrated in figure 1.5 [94S93, 93JOC3038, 95JOC3401, 95JOC638, 96JOC1624]



X = O NR

Figure 1 5

Employing the electron withdrawing and anion stabilizing properties of benzotriazole as well as its good leaving ability, systems such as **1.14** can serve as synthetic equivalents of **1.15** (figure 1 6)

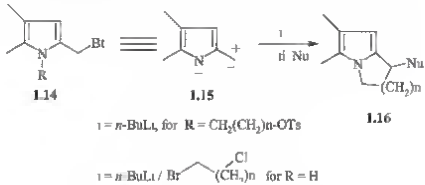


Figure 1 6

As a result of the electron withdrawing and good leaving properties of benzotriazole, the α-carbon of a side chain can behave both as an electron deficient and an electron rich center (**1.15**) While the benzotriazolyl group activates the α-hydrogen towards proton loss generating a carbanion stabilized by the electron withdrawing property of benzotriazole, its electron withdrawing property makes the α-carbon behave as an

electron deficient center, which can react with nucleophiles Thus, for example, the synthon **1.14** has two positions for lithiation, which can be manipulated individually by changing the stoichiometry of the lithiating reagent Hence when R is an alkyl group possessing a good leaving group such as a tosyl group as demonstrated in chapter 2, lithiation with 1 equivalent of base occurs at the CH_2 side chain, the carbanion thus formed is stabilized by benzotriazole Intramolecular cyclization can readily occur by nucleophilic attack of this carbanion on the carbon bearing the tosyl group, resulting in the displacement of the leaving group The benzotriazolyl group can then be displaced by nucleophiles to give **1.16** When R is hydrogen, **1.14** can be lithiated with 2 equivalents of base to generate the dianion, which reacts with 1 equivalent of an electrophile exclusively at the benzotriazole stabilized carbanion. When the electrophile has another good leaving group such as a halogen, intramolecular cyclization can also occur by nucleophilic displacement of the halogen by the nitrogen centered anion

Replacement of nitrogen in **1.14** by an oxygen gives furan systems such as **1.17** which can similarly serve as synthetic equivalents of **1.18** as reported in chapter 3 Hence, reaction of **1.17** with 1 equivalent of a base will generate the benzotriazolyl stabilized carbanion which undergoes mainly 1,4 addition with α,β-unsaturated carbonyl groups Driven by the good leaving ability of benzotriazole, acid catalyzed dehydrobenzotriazolylation readily occurs followed by cyclodehydration to give **1.19**

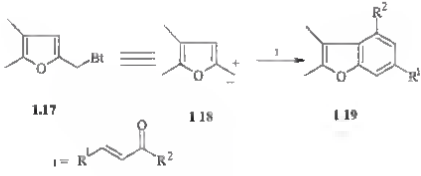


Figure 1.7

1,3-Dipolar cycloaddition reactions of azides with olefins is one of the important methods for the preparation of 1,2,3-triazolines and aziridines. The rate of the cycloaddition reaction has been reported to be dependent on the electronic nature of substituents on both the olefin and the azide [84MI559]. In chapter 4, the electron donating property of benzotriazole is applied to cycloaddition reactions. It is expected that the electron donating property of benzotriazole can stabilize the dipolarophile **1.20** and activate it toward 1,3-dipolar cycloaddition reactions with olefins (figure 1.8). The elimination of nitrogen from **1.21** to give **1.22** should also be facilitated by the electron withdrawing property of benzotriazole.

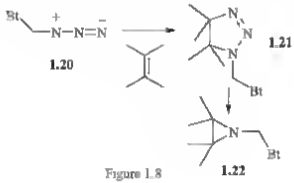


Figure 1.8

N-Substituted derivatives of benzotriazole such as **1.23** have interesting properties Due to the electron accepting properties of benzotriazole, they can dissociate to give the ion pairs **1 24** which can undergo stepwise addition to enamines enamides and enol ethers [93JOC812, 93JOC1970, 96JOC7578, 92JOC4932] In all cases, the immonium ion adds first, followed by addition of the benzotriazole anion. The addition of **1 24** to acetylenes follows a different mechanism, as demonstrated in chapter 5, in which the benzotriazolyl anion first undergoes a Michael addition followed by the addition of the immonium cation. The benzotriazole group can then be readily displaced by nucleophiles

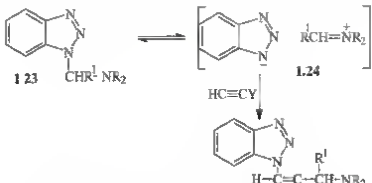
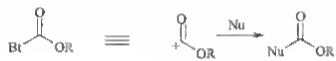


Figure 1 9 **1 25**

The good leaving group ability of the benzotriazolyl group is most fundamental in benzotriazole-mediated synthesis This is demonstrated in chapter 6, where the benzotriazolyl group serves as a better leaving group than an alkoxy group

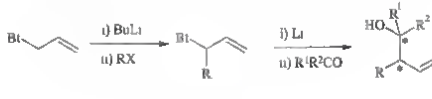


1.26 **1 27** **1 28**

Figure 1 10

Nucleophilic attack on the carbonyl carbon of **1.26** results in the elimination of the benzotriazolyl group rather than the alkoxy group, giving **1.25**. When the nucleophilic center is the nitrogen as in amino acids, this methodology serves as a useful procedure for *N*-protection of amino acids.

Methods that involve C-C bond formation with the generation of two new stereo centers are of considerable interest in organic synthesis. The synthetic application of benzotriazole as a good leaving group has been extensively explored by Katritzky and co-workers. In most cases, benzotriazole behaved as a nucleofuge producing a carbocation **1.10** which can be trapped by nucleophiles [91T2683, 94S445, 97CRip]. Recently, a new methodology was developed in which the C-Bt bond was cleaved, with the formation of a carbanion **1.13**, which can be trapped by carbonyl compounds as shown in figure 1.21. This methodology offers a new approach for the removal of the benzotriazolyl group. Chapter 7 deals with the application of this new methodology to allylbenzotriazoles.



1.29 **1.30** **131**

Figure 1.11

CHAPTER II
GENERAL AND EFFICIENT APPROACHES TO FUSED [1,2-*a*[-PYRROLES AND -INDOLES

2.1 Introduction

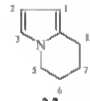
Fused [1,2-*a*]pyrrole alkaloids, including both 2,3-dihydro-*1H*-pyrrolo[1,2-*a*] pyrrole (**2.1**) and 5,6,7,8-tetrahydropyrrole[1,2-*a*]pyridine (**2.2**) derivatives (figure 2.1), are biologically active and widely distributed in nature [68MI, 77JMC812 and 90B9225] Consequently, there has been continuing interest in the synthesis of ring systems **2.1** and **2.2** [82CJC2295, 82JOC1682, 90H9, 90JOC4801, 92JOC4206, 92SC2737 and 96JOC2185] Although numerous synthetic approaches to the fused [1,2-*a*]pyrroles **2.1** and pyridines **2.2** have been described, no general route has utilized precursors of type pyrrolyl 2-CH_2X, (in which X is both an electron-withdrawing and a leaving group), to build the fused ring and, subsequently, to enable further modification by replacement of the functionality X

Due to the pharmacological importance of mitomycins [79MI, 83MI, 93CPB854], the syntheses of mitomycin skeletons and mitomycin-like compounds, such as 2,3-dihydro-*1H*-pyrrolo[1,2-*a*]indole (**2.3**) and 1,2,3,4-tetrahydropyrido[1,2 -*a*]indole (**2.4**) (figure 2.1), has attracted much attention in the search for new drugs Recent examples of the preparation of such fused [1,2-*a*]indoles **2.3** include a) facile

intramolecular radical cyclizations [91JOC3479, 93SL231, 94JOC2456, 95TL4857 and 96JCS(P1)675], ii) intramolecular cyclization by photolysis [91JA8185 and 94JOC7962], iii) classical intramolecular nucleophilic substitution [87TL6125 and 91CC892], iv) intramolecular cycloaddition reaction by thermolysis of the corresponding tosylhydrazones [88CC166], v) Dieckmann/ring expansion [91T4645], vi) a one-pot procedure *via* cyclic trialkyl(indol-2-yl)borate [92TL6849], vii) the samarium(II) iodide-promoted intramolecular hydroxyalkylations of 3-formylindoles [93CC1277], and viii) C-2-side chain modification of 2-methyl-3-alkylindoles *via* 3-methylthioindoles [85TL165]. In contrast, synthesis of 1,2,3,4-tetrahydropyrido[1,2-*a*]indole **2.4** derivatives is less explored. The recent synthetic methods for the construction of ring system **2.4** are mainly intramolecular radical cyclizations [93SL231, 94JOC2456, 95TL4857, 96JCS(P1)675], classical intramolecular nucleophilic substitution [91CC892] and the Dieckmann/ring expansion approach [91T4645].

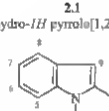
2.1

2,3-dihydro-*1H*-pyrrolo[1,2-*a*]pyrrole



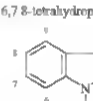
2.2

5,6,7,8-tetrahydropyrrolo[1,2-*a*]pyridine



2.3

2,3-dihydro-*1H*-pyrrolo[1,2-*a*]indole



2.4

1,2,3,4-tetrahydropyrido[1,2-*a*]indole

Figure 2.1

Previous studies in the Katritzky group have demonstrated 2-[(benzotriazol-1-yl)methyl]-pyrroles and -indoles to be versatile intermediates in the synthesis of pyrrole and indole derivatives [96JOC1624, 95JOC3401 and 96TL5641]. The important feature of 2-(benzotriazol-1-yl)methyl side chains attached to electron-rich pyrrole and indole nuclei is that the benzotriazolyl moiety behaves as both an anion stabilizing and a good leaving group. This allows a wide range of electrophiles and nucleophiles to be introduced into the 2-position by successive deprotonation, reaction with an electrophile and replacement of the benzotriazolyl group with a nucleophile.

2.2 Results and Discussion

Synthesis of 1-(Benzotriazol-1-yl)-2,3-dihydro-*1H*-pyrrolo[1,2-*a*]pyrroles (2.10a-c), 8-(Benzotriazol-1-yl)-5,6,7,8-tetrahydropyrrolo[1,2-*a*]pyridines (2.21a-b), 1-(Benzotriazol-1-yl)-2,3-dihydro-*1H*-pyrrolo[1,2-*a*]indole (1.25) and 1-(Benzotriazol-1-yl)-1,2,3,4-tetrahydropyrido[1,2-*a*]indole (1.27)

Previous work by Katritzky and co-workers showed that that 2-[(benzotriazol-1-yl)methyl]pyrroles can be easily obtained by the reaction of alkynyloxiranes, derived from 1-propargylbenzotriazole (**2.5**) and α-bromo ketones **2.6** or **2.17**, with primary amines [96JOC1624]. To construct the fused [1,2-*a*]pyrroles the intramolecular cyclization of the *N*-functionalized-alkyl-2-[(benzotriazol-1-yl)methyl]pyrroles **2.8a-c** and **2.19a-b** (figures 2.2 and 2.4) were examined, a strategy similar to that reported for the synthesis of 1,2-dihydro-*3H*-pyrrolo[1,2-*a*]pyrrole-1-carboxylic acids [82CJC2295].

This strategy called for the reaction of 2-hydroxyethylamine and 3-hydroxypropylamine with alkynyloxiranes **2.7** or **2.18**, which are available in up to 90% yields (based on GCMS) by treatment of 1-propargylbenzotriazole (**2.5**) with 1 eq of *n*-BuLi followed by reaction with an α-bromo ketone **2.6** or **2.17** at -78 °C for 12 hours. The preparation of compounds of type **2.7** and **2.18** by this method seems quite general and the scope depends on the availability of α-bromo carbonyl compounds. The compounds **2.7a-c** and **2.18a-b** were stable at room temperature, but decomposed upon heating above 60 °C. We found it effective to use alkynyloxiranes **2.7a-c** and **2.18a-b**, after aqueous workup, without further purification. They were refluxed with 2-hydroxyethylamine or 3-hydroxypropylamine in *i*-PrOH for 24-48 hours to give the corresponding pyrroles **2.8a-c** and **2.19a-b** in good yields.

An initial attempt at the transformation of **2.8a** to fused [1,2-*a*]pyrrole **2.10a** was carried out in one-pot. **2.8a** was treated with 1 eq. of LDA, followed by reaction with tosyl chloride to generate tosylate **2.9a**, which underwent intramolecular cyclization upon treatment with LDA or *n*-BuLi to give **2.10a** in fairly low yield. However, the overall yield was dramatically improved by the isolation of tosylate **2.9a** using a two-step procedure. Thus, compounds **2.8a-c** or **2.19a-b** were reacted with tosyl chloride in methylene chloride in the presence of triethylamine to afford tosylates **2.9a-c** or **2.20a-b** in high yields. The intramolecular cyclizations of **2.9a-c** and **2.20a-b** via intlusion of the benzotriazol-1-ylmethyl group and subsequent nucleophilic substitution of tosylate gave 1-(benzotriazol-1-yl)-2,3-dihydro-*1H*-pyrrolo[1,2-*a*]pyrroles **2.10a-c** and 8-(benzotriazol-1-yl)-5,6,7,8-tetrahydro-pyrrolo[1,2-*a*]pyridines **2.21a-b** in good yields. Compounds **2.21a-b** were obtained

in good purity after aqueous workup (based on ^{1}H NMR and GCMS), therefore they were used directly for synthetic manipulation without further purification

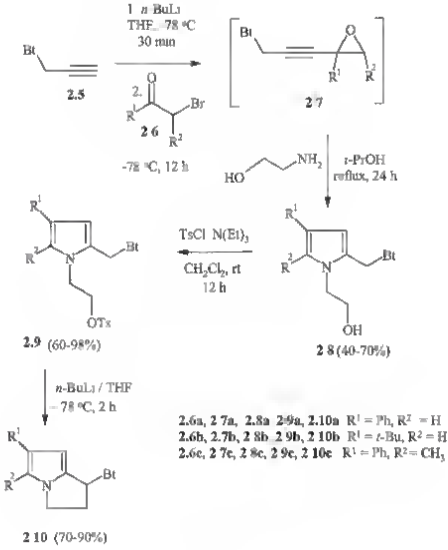


Figure 2 2

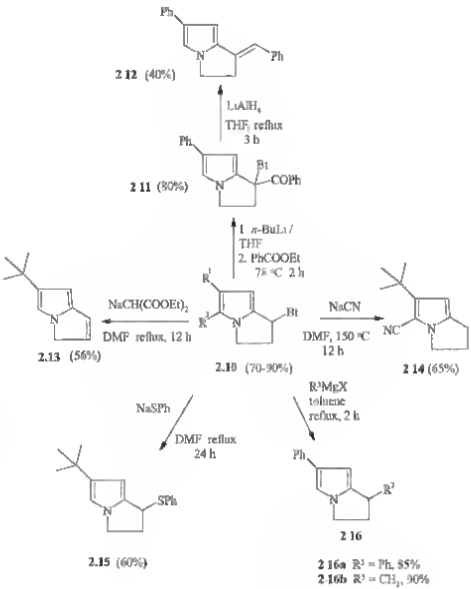

Ph
Ph
2 12 (40%)
LiAlH4
THF, reflux
3 h
Ph
Bt
COPh
2 11 (80%)
1. n-BuLi / THF
2. PhCOOEt
78 °C 2 h
R1
R2
Bt
NaCH(COOEt)2
DMF reflux, 12 h
2.13 (56%)
2.10 (70-90%)
NaCN
DMF, 150 °C
12 h
NC
2 14 (65%)
NaSPh
DMF reflux
24 h
SPh
2.15 (60%)
R3MgX
toluene
reflux, 2 h
Ph
R3
2 16
2 16a R3 = Ph, 85%
2 16b R3 = CH3, 90%

Figure 2.3

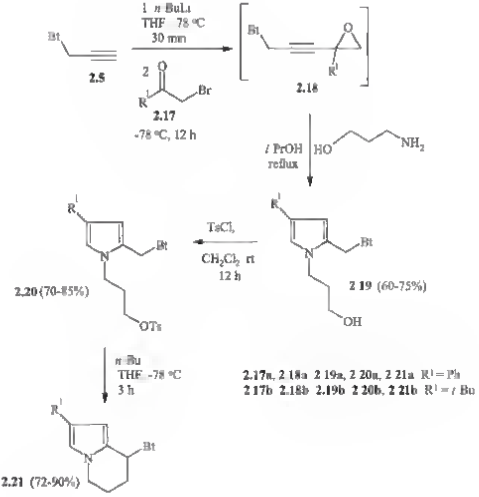

1 n-BuLi
THF -78 °C
30 min
2.5
2
2.17
-78 °C, 12 h
2.18
i PrOH
reflux
NH2
2.19 (60-75%)
TsCl,
CH2Cl2 rt
12 h
2.20 (70-85%)
n-Bu
THF -78 °C
3 h
2.21 (72-90%)
2.17a, 2.18a, 2.19a, 2.20a, 2.21a R1 = Ph
2.17b, 2.18b, 2.19b, 2.20b, 2.21b R1 = t-Bu

Figure 2.4

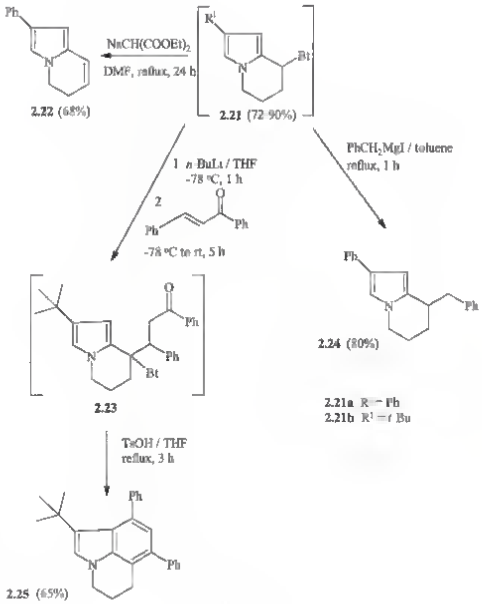

NaCH(COOEt)2
DMF, reflux, 24 h
2.22 (68%)
2.21 (72-90%)
1 n-BuLi / THF
-78 °C, 1 h
2
-78 °C to rt, 5 h
PhCH2MgI / toluene
reflux, 1 h
2.24 (80%)
2.21a R1 = Ph
2.21b R1 = t-Bu
2.23
TsOH / THF
reflux, 3 h
2.25 (65%)

Figure 2.5

2-[(Benzotriazol-1-yl)methyl]indole (**2.27**) was readily prepared from 1-propargylbenzotriazole (**2.5**) *via* a coupling reaction of the copper salt **2.26** with *ortho*-iodoaniline (figure 2.6). Lithiation of **2.27** with 2 eq. of *n*-BuLi in THF at -30 °C for 30 minutes generated dianion **2.28** previously shown to exhibit interesting reactivity on alkylation [95JOC3401]. An attempt to synthesize **2.27** by direct palladium-catalyzed reaction [92JCS(CC)41] of 1-propargylbenzotriazole (**2.5**) with *ortho*-iodoaniline failed. Dianion **2.28** should couple with a dielectrophile to form a fused five- or six-membered ring *via* [3 + 2] or [3 + 3] annulation given the proper choice of the dielectrophile. Indeed, when dianion **2.28** was treated with 1 eq. of 1-bromo-2-chloroethane at -78 °C for 3 h, followed by addition of HMPA as a co-solvent at room temperature for 12 h, 1-(benzotriazol-1-yl)-2,3-dihydro-*1H* pyrrolo[1,2-*a*]indole (**2.30**) was obtained in high yield. Similarly, 1-(benzotriazol-1-yl)-1,2,3,4-tetrahydropyrrido[1,2-*a*]indole (**2.35**) was obtained using 1-bromo-3-chloropropane as the dielectrophile. A reaction pathway through intermediate **2.29** and the *N*-lithium salt of **2.34** is supported by the isolation of compound **2.34** after treatment of **2.28** with 1-bromo-3-chloropropane at -78 °C for 3 h. The mono-alkylated compound **2.34** was transformed into **2.35** in excellent yield by intramolecular cyclization in DMSO in the presence of NaH. Significantly, the cyclizations of **2.29** and **2.34** occurred regiospecifically at the indole nitrogen and no trace of reaction at the indole 3-position was found by ^{1}H NMR or GCMS. Other functionalized dielectrophiles should enable construction of other functionalized fused ring systems.

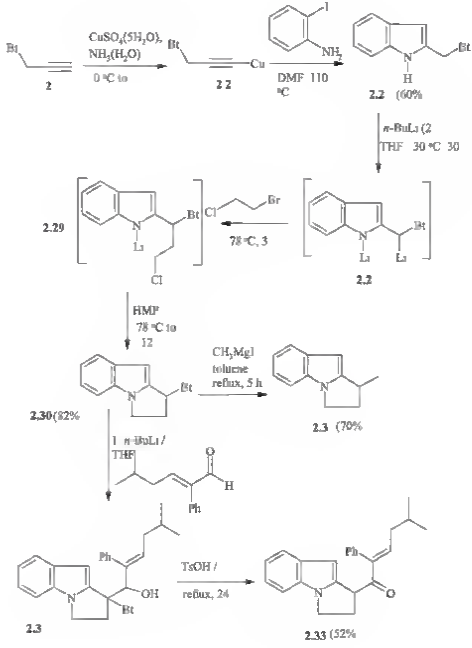

Bt
2
CuSO4(5H2O),
NH2(H2O)
0 °C to
Bt
Cu
2 2
I
NH2
DMF 110
°C
Bt
N
H
2.2 (60%
n-BuLi (2
THF 30 °C 30
Br
Cl
78 °C, 3
2.29
Bt
N
Li
Cl
Bt
N
Li
Et
2.2
HMF
78 °C to
12
CH3MgI
toluene
reflux, 5 h
2.30 (82%
2.3 (70%
1 n-BuLi /
THF
O
H
Ph
Ph
OH
Bt
2.3
TsOH /
reflux, 24
Ph
O
2.33 (52%

Figure 2 6

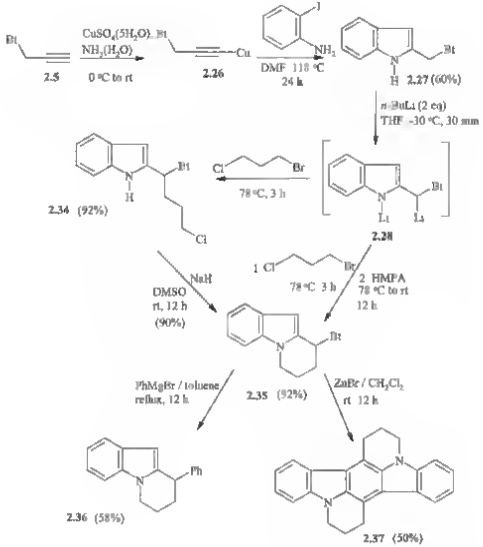

Bt
CuSO4(5H2O), Bt
NH2(H2O)
2.5
0 °C to rt
2.26
I
NH2
DMF 118 °C
24 h
Bt
N
H
2.27 (60%)
n-BuLi (2 eq)
THF -30 °C, 30 min
Cl
Br
78 °C, 3 h
Bt
N
H
2.34 (92%)
Li
Li
2.28
1 Cl
Br
78 °C 3 h
2 HMPA
78 °C to rt
12 h
NaH
DMSO
rt, 12 h
(90%)
2.35 (92%)
PhMgBr / toluene
reflux, 12 h
ZnBr / CH2Cl2
rt 12 h
Ph
2.36 (58%)
2.37 (50%)

Figure 2 7

Synthetic Manipulations of the Benzotriazol-1-yl Group Attached to Fused [1,2 -a]-pyrroles 2.10a-b, 2 21a-b and -indoles 2 30, 2.35

The synthetic versatility of 2-(benzotriazol-1-yl)methyl substituents attached to pyrroles and indoles, in terms of anion stabilization and the good leaving ability of benzotriazolyl group, have already been exploited [96JOC1624 and 95JOC3401] In the present study, the reactivity of **2.10a-b** were examined and the reactivity of **2 10c** was presumed to be similar to that of **2 10a-b**

In the pyrrole systems **2 10a-b** and **2 21a-b** nucleophilic substitutions of the benzotriazolyl group with sodium thiophenolate or Grignard reagents occurred smoothly to give the products **2.15**, **2.16a-b** and **2.24** in good yields. As in the open chain analog [96JOC1624], the reaction of **2 10b** with sodium cyanide in DMF at 150 °C afforded the "abnormal" product **2.14** (65% yield), in which the cyano group added to the 5-position of the pyrrole ring Surprisingly, unlike the open chain case [96JOC1624], treatment of **2.10b** and **2 21a** with sodium malonate in refluxing DMF gave the corresponding elimination products **2.13** and **2 22** instead of the expected substitution products Moreover, use of sodium hydride and potassium *tert*-butoxide as bases did not give any reaction and the starting materials **2 10b** and **2 21b** were recovered The partially unsaturated products **2 13** and **2 22** were not stable and they decomposed after several days at room temperature, upon exposure to air

Due to the anion stabilizing ability of the benzotriazolyl group, the intermediates **2 10a-b** and **2.21a-b** were transformed into various functionalized fused [1,2-*a*]pyrroles by sequential lithiation, alkylation and substitution of the benzotriazolyl group, as exemplified in the syntheses of compounds **2.12** and **2.25**

The compound **2.10a** was acylated by treatment with *n*-butyllithium, followed by the reaction with ethyl benzoate to form the intermediate **2.11** (in 80% yield) which was reacted with lithium aluminum hydride in THF to form the phenylmethylene attached fused [1,2-*a*]pyrrole **2.12**. The reaction pathway probably involved reduction of the carbonyl and benzotriazolyl groups, and subsequent elimination of the hydroxy group. The structure of the isolated *trans* isomer **2.12** was confirmed by NOE experiments. Similar to the open chain analog [96TL5641], the lithium derivative of compound **2.21b** was reacted with *trans* chalcone to give adduct **2.23**, which was refluxed with *p*-toluenesulfonic acid in THF to give the tricyclic fused indole **2.25**.

Apparently, the benzene ring in fused[1,2-*a*]indole systems **2.30** and **2.35** induces, as compared to the pyrrole analogs **2.10** and **2.21**, less effective cation formation at benzotriazolyl attached carbons in compounds **2.30** and **2.35**, which are thus less susceptible to nucleophilic substitution than **2.10** and **2.21**. Hence, no reactions of **2.30** and **2.35** occurred with sodium thiophenolate or sodium cyanide. However, Grignard reagents converted **2.30** and **2.35** into products **2.31** and **2.36** respectively, in good yields. Interestingly, the reaction of the lithium derivative of compound **2.30** with 5-methyl-2-phenyl-2-hexenal gave the 1,2-addition intermediate **2.32** which upon treatment with *p*-toluenesulfonic acid in THF formed the insertion product **2.33** [95JACS12015]. Compound **2.35** also underwent zinc bromide-promoted dimerization followed by dehydrogenation on exposure to air, to give the fused indolo[3,2-*b*]carbazole **2.37** in 50% yield. The novel structure **2.37** is related to compounds possessing interesting biological activity [86M11673].

In conclusion, general and efficient syntheses of fused [1,2-*a*]-pyrroles and -indoles have been described. These approaches started from readily available starting materials and involved ring synthesis of benzotriazolyl attached fused[1,2-*a*]pyrroles **2.10** and **2.21** *via* intramolecular cyclizations and fused [1,2-*a*]indoles **2.30** and **2.35** *via* [3 + 2] and [3 + 3] annulations. The intermediates **2.10**, **2.21**, **2.30** and **2.35** were further transformed by alkylation and replacement of the benzotriazolyl group to provide a variety of functionalized fused [1,2-*a*]-pyrrole and -indole derivatives. Moreover, 3-unsubstituted positions of pyrrole and indole rings allow further synthetic manipulations. Thus, the present methods provide general and efficient synthetic routes to many pyrrole and indole derivatives.

2.3 Experimental

Melting points were determined on a hot-stage microscope and are uncorrected. ^{1}H and NOE NMR spectra were recorded on a 300 MHz spectrometer using TMS as the internal standard and $CDCl_3$ as the solvent. ^{13}C NMR spectra were recorded at 75 MHz on the same instrument with the solvent peak ($CDCl_3$) as the reference. HRMS and elemental analyses (C, H, N) were carried out within the department.

1-Propargylbenzotriazole (**2.5**) [92LA843] and 2-(benzotriazol-1-yl)methylindole (**1.23**) [95JOC3401] were prepared according to previously reported procedures.

General Procedure for the Preparation of 2-[(Benzotriazol-1-yl)methyl]-pyrroles 2.8a-c and 2.19a-b

To a solution of 1-propargylbenzotriazole (**2.5**) (3.2 g, 20 mmol) in THF (100 mL) was added a solution of *n*-BuLi (20 mmol, 12.5 mL, 1.6 M in hexane) at -78 °C, the solution was stirred at this temperature for 30 min. A solution of an appropriate α-bromo ketone **2.6** or **2.17** (20 mmol) in THF (10 mL) was added and the reaction mixture was stirred at -78 °C for 20 h. A saturated NH_4Cl solution (100 mL) was added and the solution was extracted with diethyl ether (200 mL). The organic phase was separated, washed with saturated NH_4Cl solution (3 x 100 mL) and dried ($MgSO_4$).

After removal of the solvent, the residue was dissolved in *i*-PrOH, 2-hydroxyethylamine or 3-hydroxypropylamine (40 mmol) added, and the solution was refluxed for 24 h. *i*-PrOH was removed and the residue subjected to column chromatography or recrystallization to afford the corresponding product **2.8a-c** and **2.19a-b**.

***N*-(2-Hydroxy)ethyl-2-(benzotriazol-1-yl)methyl-4-phenylpyrrole 2.8a** purified by recrystallization from EtOAc/hexane (1:3), white micro crystals, yield 65%, mp 142-143 °C, ^{1}H NMR δ 7.98 (d, J = 8.3 Hz, 1 H), 7.73 (d, J = 8.3 Hz, 1 H), 7.44 (d, J = 7.2 Hz, 1 H), 7.43-7.48 (m, 1 H), 7.32-7.37 (m, 1 H), 7.24-7.29 (m, 2 H), 7.13 (d, J = 2.0 Hz, 1 H), 7.06-7.14 (m, 1 H), 6.60 (d, J = 2.0 Hz, 1 H), 6.00 (s, 2 H), 4.94 (t, J = 5.2 Hz, 1 H), 4.07 (t, J = 5.4 Hz, 2 H), 3.60 (q, J = 5.2 Hz, 2 H), ^{13}C NMR δ 145.4, 134.9, 132.2, 128.2, 126.9, 126.4, 124.8, 124.0, 123.5, 122.6, 119.6, 118.9,

110 3, 107 6, 61 3, 48 9, 43 8 Anal calcd for $C_{21}H_{19}N_4O$ C, 71 68, H, 5 70, N, 17 60 Found C, 72 10, H, 5 68, N, 17 80

***N*-(2-Hydroxy)ethyl-2-(benzotriazol-1-yl)methyl-4-(*t*-butyl)pyrrole 2.8b** purified by column chromatography using EtOAc/hexane (1 1) as the eluent, white powder, yield 70% mp 102 104 °C, ^{1}H NMR δ 8 00 (d, J = 8 2 Hz, 1 H) 7 30-7 45 (m, 3 H), 6 51 (d, J = 2 0 Hz, 1 H), 6 31 (d, J = 2.0 Hz, 1 H), 5 85 (s, 2 H), 4 00 (t, J = 5 4 Hz, 2 H), 3 61 (q, J = 5 4, 2 H), 2.28 (t, J = 5 4 Hz, 1 H), 1.23 (s, 9 H), ^{13}C NMR δ 146 2, 135 1 132.8, 127 4, 124 1, 124 0, 119 8, 118 4, 110 2, 109.3, 62.6, 48 9, 45 0, 31 7, 30 5 Anal calcd for $C_{17}H_{20}N_4O$ C, 68 43, H, 7 43 N, 18 78 Found C, 68 49, H, 7 55, N, 18 93

***N*-(2-Hydroxy)ethyl-2-(benzotriazol-1-yl)methyl-4-phenyl-5-methylpyrrole 2 8e** purified by column chromatography using EtOAc/hexane (3 7) as the eluent, white powder, yield 40% mp 171 173 °C, ^{1}H NMR δ 8 05 (d, J = 8 3 Hz, 1 H), 7 59 (d, J = 8 3 Hz, 1 H), 7 33 7 46 (m, 6 H), 7.21-7 27 (m, 1 H), 6 51 (s, 1 H), 5 97 (s, 2 H), 4 14 (t, J = 5 8 Hz, 2 H), 3 64 (q, J = 5 6 Hz, 2 H), 2 32 (s, 3 H), 1 95 (t, J = 5 7 Hz, 1 H), ^{1}C NMR δ 145 6, 136 3, 132 3, 127 8, 127 4, 126 7, 126 5, 124 7, 123 9, 123 4, 120 9, 119 1, 109 9, 109 7, 61 1, 10 6 Anal calcd for $C_{20}H_{20}N_4O$ C, 72.27, H, 6 06, N 16 85 Found C, 72.23, H 6 14, N 16 87

***N*-(3-Hydroxy)propyl-2-(benzotriazol-1-yl)methyl-4-phenylpyrrole 2 19a** purified by column chromatography using EtOAc/hexane (3 7) as the eluent, yellow oil, yield 60% ^{1}H NMR δ 8 02 (d, J = 8 1 Hz, 1 H), 7 48 (d, J = 8 5 Hz, 2 H), 7 47-7 53 (m, 1 H), 7.30-7 40 (m, 4 H), 7 19 (t, J = 8 7 Hz, 1 H), 7 01 (s, 1 H), 6.64 (d, J = 1 7 Hz, 1 H), 5 87 (s, 2 H), 4.09 (t, J = 6 8 Hz, 2 H), 3 56 (t, J = 5.5 Hz, 2 H), 1 75

(t, J = 6 3 Hz, 2 H), ^{13}C NMR δ 145 0, 135 0, 132 6, 128 5, 127 4, 125 5, 125 4, 124 7, 124 0, 123 9, 119 6, 110 1, 108 6, 58 6, 44 6, 43 3, 33 7 Anal calcd for $C_{20}H_{20}N_4O$ C, 72.27, H, 6 06, N, 16 85 Found C, 72 00, H, 6 12, N, 16 92

***N*-(3-Hydroxy)propyl-2-(benzotriazol-1-yl)methyl-4-(*t*-butyl)pyrrole 2 19b** purified by column chromatography using EtOAc/hexane (3 7) as the eluent, white powder, yield 75% mp 83 85 °C, ^{1}H NMR δ 8 01 (d, J = 8.2 Hz, 1 H), 7.31-7 46 (m, 3 H), 6 48 (s, 1 H), 6 29 (d, J = 1 7 Hz, 1 H), 5 83 (s, 2 H), 3 98 (t, J = 7 2 Hz, 2 H), 3 55 (t, J = 5 9 Hz, 2 H), 2 43 (brs, 1 H), 1 64-1 69 (m, 2 H), 1 23 (s, 9 H), ^{13}C NMR δ 146 2 135 0, 132 8, 127 3, 124 0, 123 7, 119 7, 117 9, 110.3, 108 9, 59 2, 45 0, 43 2, 33 9, 31 7, 30.5 Anal calcd for $C_{19}H_{24}N_4O$ C, 69.20 H, 7 74, N, 17 93 Found C, 69 57, H 7 76, N 17 90

General Procedure for the Preparatioo of Tosylate 2.9a-c ood 2.20a-b

To a solution of compound **2.8** or **2.19** (10 mmol) in methylene chloride (60 mL), triethyl amine (15 mL) was added *P*-Toluenesulfonic acid chloride (5 87 g, 30 mmol) was added in portions over a period of 1 h and the reaction mixture was stirred at room temperature overnight. The reaction solution was washed with 2 N HCl solution (50 mL), followed by 10 % $NaHCO_3$ solution (50 mL) and water (3 x 50 mL) The organic layer was separated, dried ($MgSO_4$) and the solvent removed to give the product **2 9a-c** or **2.20a-b**

***N*-(2-Tosyl)ethyl-2-(benzotriazol-1-yl)methyl-4-phenylpyrrole 2.9a** purified by recrystallization from EtOAc/hexane (1 1), white powder, yield 98% mp 121-122 °C, ^{1}H NMR δ 8 03 (d, J = 8 1 Hz, 1 H), 7 51 (d, J = 8 3 Hz, 3 H), 7 46-7 33 (m, 6 H), 7.21 (t, J = 7.2 Hz, 1 H), 7 09 (d, J = 8 5 Hz, 2 H), 6 81 (d, J = 1 9 Hz, 1 H), 6 59 (d, J

1 9 Hz, 1 H), 5 78 (s, 2 H), 4 20 (t, J = 4 7 Hz 2 H), 4 01 (t, J = 4 7 Hz, 2 H), 2.25 (s, 3 H), ^{13}C NMR δ 146 2, 144 9, 134.6, 132 4, 131 8, 129 7, 128 6, 127.5, 125 8, 125 7, 124 7, 124 5, 124 0, 119 8 119 7, 109 9, 109 2, 69 0, 45 4, 44 2, 21 4 Anal calcd for $C_{26}H_{24}N_4O_3S$ C, 66 08, H, 5 12, N, 11 86 Found. C, 66 08, H, 5 08, N, 11 86

***N*-(2-Tosyl)ethyl-2-(benzotriazol-1-yl)methyl-4-(*t*-butyl)pyrrole 2.9b** purified by recrystallization from EtOAc/hexane (1 1), white needles, yield 98% mp 96-98 °C, ^{1}H NMR δ 8 03 (d, J = 8.2 Hz, 1 H), 7 61 (d, J = 8 3 Hz, 2 H), 7 33-7 44 (m, 3 H), 7 26 (d, J = 8 1 Hz, 2 H) 6 41 (d, J = 2 0 Hz 1 H), 6 28 (d, J = 2 0 Hz, 1 H), 5 74 (s, 2 H) 4 16 (t, J = 5 3 Hz, 2 H), 3 96 (t, J = 5 3 Hz, 2 H), 2 43 (s, 3 H), 1.22 (s, 9 H), ^{13}C NMR δ 146 3, 144 6, 135.4, 132 6, 132 4 129 8, 127 7, 127 4, 124 0, 123 9, 119.9, 118 6, 110 0, 109 6, 69 1 45 3, 44 6, 31 6 , 30 4, 21 6 Anal. calcd for $C_{24}H_{28}N_4O_3S$ C, 63 69, H, 6.24, N, 12.38 Found C, 63 69, H, 6.24, N, 12.38

***N*-(2-Tosyl)ethyl-2-(benzotrinzol-1-yl)methyl-4-phenyl-5-methylpyrrole 2.9c** purified by recrystallization from EtOAc/hexane (1 1), white powder, yield 60% mp°C, ^{1}H NMR δ 8 02 (d, J = 8 1 Hz, 1 H), 7 44-7 59 (m, 2 H), 7 20-7 42 (m, 10 H), 6 44 (s, 1 H) 5 82 (s, 2 H), 4 25 (t, J = 5 1 Hz, 2 H), 4 03 (t, J = 5 3 Hz, 2 H) 2.34 (s, 3 H), 2 15 (s, 3 H), ^{13}C NMR δ 146 2, 144 9, 136.2, 132.5, 131 9, 129 8, 128 3, 127 8, 127 6, 127 4 127 1, 125.5, 123 9, 123 8, 122.0, 119 8, 111.2, 110 0 68.3, 45 7, 44 6 Anal calcd for $C_{27}H_{28}N_4O_3S$ C, 66 65, H, 5.39, N, 11 51

***N*-(3-Tosyl)propyl-2-(benzotrinzol-1-yl)methyl-4-phenylpyrrole 2.20a** purified by column chromatography using EtOAc/hexane (1 1) as the eluent, white powder, yield 85% mp 101 102 °C, ^{1}H NMR δ 8 02 (d, J = 8 2 Hz, 1 H). 7 76 (d, J = 8.3 Hz, 2 H),

7.25-7.49 (m, 9 H), 7.18 (t, J = 7.3 Hz, 1 H), 6.87 (d, J = 2.0 Hz, 1 H), 6.66 (d, J = 2.0 Hz, 1 H), 5.81 (s, 2 H), 3.98 (t, J = 6.9 Hz, 2 H), 3.90 (t, J = 5.7 Hz, 2 H), 2.41 (s, 3 H), 1.70-1.74 (m, 2 H), ^{13}C NMR δ 146.0, 145.0, 134.8, 132.6, 129.9, 128.7, 127.8, 127.7, 125.8, 125.1, 124.9, 124.4, 124.3, 119.8, 110.1, 109.5, 66.7, 44.7, 42.9, 30.4, 21.6. Anal. calcd for $C_{27}H_{26}N_4O_3S$: C, 66.65; H, 5.39; N, 11.51. Found: C, 66.66; H, 5.56; N, 11.63.

***N*-(3-Tosyl)propyl-2-(benzotriazol-1-yl)methyl-4-(*t*-butyl)pyrrole 2.20b** purified by column chromatography using EtOAc/hexane (3:7) as the eluent, white powder, yield 70%; mp 83-85°C; ^{1}H NMR δ 8.02 (d, J = 8.2 Hz, 1 H), 7.78 (d, J = 8.1 Hz, 2 H), 7.33-7.42 (m, 5 H), 6.37 (d, J = 1.7 Hz, 1 H), 6.23 (d, J = 1.7 Hz, 1 H), 5.74 (s, 2 H), 3.87-3.91 (m, 4 H), 2.45 (s, 3 H), 1.65-1.69 (m, 2 H), 1.21 (s, 9 H); ^{13}C NMR δ 146.3, 144.9, 135.2, 132.7, 129.9, 128.9, 127.9, 127.4, 123.9, 123.6, 119.9, 118.2, 110.1, 109.5, 67.0, 44.8, 42.6, 31.6, 30.5, 30.4, 21.6. Anal. calcd for $C_{25}H_{30}N_4O_3S$: C, 64.35; H, 6.48; N, 12.01. Found: C, 64.36; H, 6.42; N, 12.68.

General Procedure for the Preparation of Fused [1,2-*a*]pyrroles 2.10a-c and 2.21a-b

To a solution of tosylate **2.9** or **2.20** (10 mmol) in THF (80 mL) was added a solution of *n*-BuLi (10 mmol, 6.25 mL, 1.6 M in hexane) at -78 °C. The reaction mixture was stirred and allowed to warm to room temperature overnight. The reaction was quenched with saturated NH_4Cl solution (50 mL), extracted with EtOAc, washed with brine (3 x 50 mL) and dried ($MgSO_4$). The solvent was removed to give the crude product which was purified by column chromatography to give the corresponding compound **2.10a-c**. The crude products **2.21a-c** were used directly for the synthesis of

compounds **2 22**, **2.24-2.25** without further purification and the yields were determined by GCMS (Scheme 2 5)

1-(Benzotriazol-1-yl)-6-phenyl-2,3-dihydro-*1H*-pyrrolizine 2 10a purified by column chromatography using EtOAc/hexane (1.2) as the eluent, yellow oil, yield 75%. ^{1}H NMR δ 8 02-8 08 (m, 1 H), 7 48 (d, *J* =7.2 Hz, 2 H), 7 30-7.34 (m 4 H), 7 15-7 19 (m, 2 H), 6 65-6 69 (m, 1 H), 6.55 (dd, *J* = 8 0 and 2 7 Hz, 1 H), 6 33 (s, 1 H), 4 26-4 35 (m, 1 H), 4.15-4 22 (m, 1 H), 3 20-3 32 (m, 1 H), 2 78-2 87 (m, 1 H), ^{13}C NMR δ 146.4, 135 7, 132.8, 131.7, 130 7, 128 6, 127 4, 125 7, 124 9, 123 8, 119 9, 112.3, 109 7, 100 8, 56 5, 45 4, 36 3 Anal calcd for $C_{19}H_{17}N_4O$ C, 75 72, H, 5 69, N, 18 59. Found C, 75 38, H, 5 31, N, 18 41

1-(Benzotriazol-1-yl)-6-(*t*-butyl)-2,3-dihydro-*1H*-pyrrolo[1,2-*a*]pyrrole 2 10b purified by column chromatography using EtOAc/hexane (1.2) as the eluent, yellow oil, yield 90% ^{1}H NMR δ 8 02-8 06 (m, 1 H), 7 27-7.35 (m, 2 H), 6 68 (d, *J* = 1 4 Hz, 1 H), 6 50-6 53 (m, 1 H), 6.34-6 39 (m, 1 H), 5 98 (d, *J* = 1 4 Hz, 1 H), 4 09-4 23 (m, 2 H), 3 18-3 31 (m, 1 H), 2 71-2 80 (m, 1 H),1.25 (s, 9 H), ^{13}C NMR δ 146 3, 142 4, 131 8, 131 3, 127.2, 123 7, 119 9, 110 8, 110 0, 100 9, 56 9, 45 2, 36 7, 31 9, 31 1 Anal calcd for $C_{17}H_{20}N_4$ C, 72 83, H, 7 19, N 19 98 Found C, 72.55, H 7 44, N, 20 31

1-(Benzotriazol-1-yl)-5-methyl-6-phenyl-2,3-dihydro-*1H*-pyrrolo[1,2-*a*]pyrrole 2.10e purified by column chromatography using EtOAc/hexane (1 2) as the eluent, yellow oil, yield 70% ^{1}H NMR δ 8 03-8 06 (m, 1 H) 7 28-7 41 (m, 6 H), 7 16-7.22 (m, 1 H), 6 81-6 85 (m 1 H), 6 50 (dd, *J* = 8 0 Hz and 2 7 Hz, 1 H), 6 17 (s, 1 H), 4.06-4.25 (m, 2 H), 3 18-3 38 (m, 1 H), 2 85-2 95 (m, 1 H), 2 46 (s, 3 H), ^{13}C NMR δ

146.3, 136.9, 131.7, 129.5, 128.2, 127.3, 127.2, 126.4, 125.2, 123.7, 121.4, 119.8, 109.8, 102.2, 56.6, 43.4, 35.9, 11.2. Anal. calcd for $C_{17}H_{20}N_4$: C, 76.41; H, 5.77; N, 17.82. Found: C, 76.18; H, 6.00; N, 17.59.

Preparation of 1-(Benzotriazol-1-yl)-1-phenylcarbonyl-6-phenyl-2,3-dihydro-*1H*-pyrrolo[1,2-*a*]pyrrole 2.11

To a solution of compound **2.10a** (0.97 g, 3.2 mmol) in THF (80 mL), a solution of *n*-BuLi (2 mL, 3.2 mmol, 1.6 M in hexane) was added at -78 °C. After 30 min, ethyl benzoate (0.48 g, 3.2 mmol) was added and the reaction mixture was allowed to warm to room temperature overnight. The reaction was quenched with saturated NH_4Cl solution (100 mL), extracted with EtOAc (100 mL) and dried ($MgSO_4$). The solvent was removed and the product isolated as yellow needles (1.03 g, 80% yield) by column chromatography using EtOAc/hexane (1:2) as the eluent. mp 175-178 °C; ^1H NMR δ 8.05-8.08 (m, 1 H), 7.67 (d, J = 8.6 Hz, 2 H), 7.44-7.47 (m, 3 H), 7.29-7.38 (m, 6 H), 7.15-7.21 (m, 2 H), 6.62-6.67 (m, 1 H), 6.48 (s, 1 H), 4.24-4.32 (m, 1 H), 4.10-4.20 (m, 1 H), 2.91-2.99 (m, 1 H). ^{13}C NMR δ 190.0, 146.4, 135.3, 133.8, 133.4, 131.9, 130.6, 130.4, 129.6, 128.7, 128.5, 128.1, 126.1, 125.2, 124.3, 120.4, 113.9, 110.6, 105.1, 74.2, 45.1, 41.0. Anal. calcd for $C_{24}H_{20}N_4O$: C, 77.21; H, 4.98; N, 13.85. Found: C, 77.27; H, 5.00; N, 13.65.

Preparation of 1-Phenylmethylene-6-phenyl-2,3-dihydro-*1H*-pyrrolo[1,2-*a*]-pyrrole 2.12

To a solution of $LiAlH_4$ (0.087 g, 2.3 mmol) in THF (30 mL) was added a solution of compound **2.11** (0.45 g, 1.1 mmol) at room temperature and the reaction mixture was refluxed for 4 h. After cooling, ethyl acetate (50 mL) and water (50 mL) were added.

The organic layer was separated, washed with water (3 x 50 mL) and dried ($MgSO_4$). The solvent was evaporated off and the solid residue was washed with diethyl ether to give the product **2.12** (0.12 g, 40 % yield) as white powder: mp 188-189 °C, ^1H NMR δ 7.53 (d, J = 7.7 Hz, 2 H), 7.31-7.37 (m, 6 H), 7.17-7.23 (m, 2 H), 7.03 (s, 1 H), 6.74 (d, J = 1.9 Hz, 1 H), 6.56 (s, 1 H), 4.16 (t, J = 6.3 Hz, 2 H), 3.45 (t, J = 6.3 Hz, 2 H), ^{13}C NMR δ 140.1, 138.1, 136.1, 131.6, 128.6, 128.5, 128.0, 126.0, 125.6, 125.1, 117.3, 113.0, 111.2, 96.1, 45.5, 33.2. Anal. calcd for $C_{20}H_{17}N$: C, 88.52; H, 6.32; N, 5.16. Found: C, 88.74; H, 6.42; N, 5.25.

Preparation of 5-Cyano-6-(*t*-butyl)-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]pyrrole 2.14

A solution of **2.10b** (0.60 g, 2.14 mmol) and NaCN (0.51 g, 10 mmol) in DMF (30 mL) was refluxed for 12 h. After cooling, diethyl ether (50 mL) and water (50 mL) were added and the organic phase was separated, washed with NaOH solution (2 N, 2 x 50 mL), and dried ($MgSO_4$). After removal of the solvent under reduce pressure, the residue was purified by column chromatography using CH_2Cl_2/hexane (1:4) as the eluent to give the product **2.14** as a yellow oil (0.62 g, 65%). ^1H NMR δ 5.79 (s, 1 H), 3.88-3.96 (m, 2 H), 2.73-2.91 (m, 2 H), 2.50 (t, J = 7.4 Hz, 2 H), 1.34 (s, 9 H), ^{13}C NMR δ 151.0, 141.6, 115.7, 99.5, 46.4, 32.0, 31.9, 31.0, 26.5. HRMS calcd. for $C_{12}H_{16}N_2$: 188.1313 (M$^+$). found: 188.1321.

General Procedure for the Preparation of 6-*t*-Butyl-3-hydro-1*H*-pyrrolo[1,2-*a*]pyrrole 2.13 and 2-Phenyl-5,6-dihydropyrrolo[1,2-*a*]pyridine 2.22.

To a solution of diethyl malonate (0.34 g, 2 mmol) in DMF was added sodium hydride (0.08 g, 2 mmol) at room temperature. After being stirred for 30 minutes, compound **2.10b** or **2.21a** (1 mmol) in DMF (5 mL) was added and the reaction

mixture was refluxed for 12 to 24 h After cooling, diethyl ether (50 mL) and water (50 mL) were added and the organic phase was separated, washed with water (3 x 30 mL) and dried ($MgSO_4$). The solvent was removed under reduced pressure, and the residue was separated by column chromatography using CH_2Cl_2/hexane (1 4) to afford the correspondiog **2.13** or **2 22**

6-*t*-Butyl-3-hydro-*1H*-pyrrolo[1,2-*a*]pyrrole 2.13 yellow oil, 56% yield ^1H NMR δ 6.87 (s, 1 H), 6 22 (d, J = 8 9 Hz, 2 H), 5 79 (s, 1 H), 4 43 (s, 2 H), 1.21 (s, 9 H), ^{13}C NMR δ 153 3, 141 7, 116 1, 114 9, 111 2, 95 9 50 9, 32 9, 30 1 HRMS calcd for $C_{12}H_{15}N$ 161 1205 (M^+), found 161 1205

2-Phenyl-5,6-dihydropyrrolo[1,2-*a*]pyridine 2.22 yellow oil, 68% yield ^1H NMR δ 7 49 (d, J = 7 1 Hz, 2 H), 7 31 (t, J = 7 6 Hz, 2 H) 7 15 (t, J = 7 3 Hz, 1 H), 6 86 (d, J = 1 6 Hz, 1 H), 6 45 (d, J = 9 8 Hz, 1 H), 6 31 (d, J = 1.6 Hz, 1 H), 5 71-5 77 (m, 1 H), 3 97 (t, J = 7 2 Hz, 2 H), 2 48-2 55 (m, 2 H); ^{13}C NMR δ 135 8, 130 2, 128 6, 125 3, 124.9, 122.4, 120 1, 119 5, 117 8, 103 7, 43 8, 24.4 HRMS calcd. for $C_{14}H_{13}N$, 195 1048 (M^+), found 195 1075

Preparation of 1-Thiophenyl-6-(*t*-butyl)-2,3-dihydro-*1H*-pyrrolo[1,2-*a*]pyrrole 2.15

A solution of **2 10b** (0 50 g, 2 mmol) and sodium thiophenolate (0 66g, 5 mmol) in DMF (50 mL) was refluxed for 24 h After cooling, water (50 mL) and diethyl ether (100 mL) were added and the organic phase was separated, washed with water (3 x 50 mL) and dried ($MgSO_4$) The solvent was removed under reduced pressure and the residue was separated by column chromatography using CH_2Cl_2/hexane (1 4) as the eluent to give the product **1-31** as a yellow oil (0 33 g, 60 % yield) ^1H NMR δ 7 50

(d, J = 8 2 Hz, 1 H), 7.34-7 40 (m, 2 H), 7.22-7 33 (m, 2 H), 6.39 (d, J = 1.5 Hz, 1 H), 5 83 (d, J = 1.5 Hz, 1 H), 4 69 (dd, J = 7.5 and 2.9 Hz, 1 H), 3 82-3 94 (m, 2 H), 2 85-2 97 (m, 1 H), 2.47-2.56 (m, 1 H), 1.23 (s, 9 H), ^{13}C NMR δ 141 1, 135 4, 135 3, 131 9, 129 1, 128 8, 127 6, 127.2, 127 0, 109 7, 98 9, 44 9, 44 4, 36.5, 31 9, 31 1 Anal calcd for $C_{17}H_{21}NS$ C, 75 23, H, 7 80, N, 5 16 Found C, 74 56, H, 7 78, N, 5 47

General Procedure for the Nucleophilic Substitution of 2 10a and 2.21e with Grignard Reagents

To a solution of **2 10a** or **2.21e** (2 mmol) in toluene (30 mL) under argon was added a solution of an appropriate Grignard reagent (Schemes 1 and 2) (4 mmol) in Et_2O, and the reaction mixture was refluxed for 1 h. The solvent was removed under reduced pressure and the residue was extracted with Et_2O (2 x 50 mL) The combined diethyl ether solution was washed with water (2 x 50 mL) and dried ($MgSO_4$) After removal of the solvent, the residue was purified by column chromatography using CH_2Cl_2/hexane (1 4) as the eluent to give the corresponding product **2.16a-h** or **2.24**

1,6-Diphenyl-2,3-dihydro-*1H*-pyrrolo[1,2-*a*]pyrrole 2 16a yellow oil, 85% yield ^{1}H NMR δ 7 50 (d, J = 7 1 Hz, 2 H), 7 20-7 38 (m, 7 H), 7 14 (t, J = 7 4 Hz, 1 H), 6 99 (s, 1 H), 6 14 (d, J = 1 0 Hz, 1 H), 4 40 (t, J = 7 7 Hz, 1 H), 4 11-4 16 (m, 1 H), 3 95-4 10 (m, 1 H), 2.91-2 97 (m, 1 H), 2.39-2 45 (m, 1 H), ^{13}C NMR δ 143 4, 140 4, 136 5, 129 4, 128 6, 128 5, 127 4, 126 7, 125 2, 124 9, 110 7, 98 4, 45 9, 43 6, 38 6 HRMS calcd for $C_{18}H_{17}N$, 259 1361 (M^+), found 259 1358

1-Methyl-6-phenyl-2,3-dihydro-*1H*-pyrrolo[1,2-*a*]pyrrole 2 16h yellow oil, 90% yield ^{1}H NMR δ 7 51 (d, J = 7 1 Hz, 2 H), 7 32 (t, J = 7 7 Hz, 2 H), 7 14 (t, J = 7 4

Hz, 1 H), 6 88 (d, J = 1 5 Hz, 1 H), 6 14 (d, J = 1.2 Hz, 1 H), 4 00-4 06 (m, 1 H), 3 86-3 98 (m, 1 H), 3 21-3 34 (m, 1 H), 2 57-2 71 (m, 1 H) 2 00-2 12 (m, 1 H), 1.34 (d, J = 6 9 Hz, 3 H), ^{13}C NMR δ 143 3, 136 4 128 9, 128 4, 125 0, 124 9, 110 2, 96 2, 45 9 36 7, 32 2, 19 7 HRMS calcd For $C_{24}H_{15}N$, 197 1205 (M^+), found 197 1267

2-Phenyl-8-benzyl-5,6,7,8-tetrahydropyrrolo[1,2-a]pyridine 2.24 yellow oil, 80% yield ^{1}H NMR δ 7 48 (d, J = 7.1 Hz, 2 H), 7 09-7 36 (m, 8 H), 6 80 (d, J = 1 7 Hz, 1 H), 6.26 (d, J = 1 7 Hz, 1 H), 3 81-3 97 (m, 2 H), 3 30 (dd, J = 13 5 and 5 0 Hz, 1 H), 3 04-3 07 (m, 1 H), 2 68 (dd, J = 13.5 and 9 8 Hz, 1 H), 1 94-2 00 (m, 1 H), 1 74 1 85 (m, 2 H) 1 34-1 39 (m 1 H), ^{13}C NMR δ 140 0, 136 1, 134 5, 129 2, 128 4, 128 3, 126 1, 125 1, 124 9, 124 2, 115 6, 102.0, 45 4, 41 8 36 1, 26 7, 22.5 HRMS calcd. for $C_{21}H_{21}N$, 288 1752 (M^+), found 288 1745

Preparation of Fused Iodole 2.25

To a solution of compound **2.21b** (0 80 g, 2 7 mmol) in THF (100 mL) was added a solution of *n* BuLi (1 69 mL, 1 6 M in hexane) at -78 °C and the reaction mixture was stirred at this temperature for 30 minutes A solution of *trans*-chalcone ((0 60 g, 2.7 mmol) in THF (10 mL) was added and the reaction mixture was stirred and allowed to warm to room temperature overnight The reaction was quenched with saturated NH_4Cl solution (100 mL) and ethyl acetate (100 mL) added. The organic phase was separated, washed with water (3 x 100 mL) and dried ($MgSO_4$) The solvent was removed under reduced pressure to give the crude oily product **2.23** which was dissolved in THF (100 mL) To the solution of **2.23** was added *p*-toluenesulfonic acid monohydrate (0 19 g, 1 mmol) and the reaction mixture refluxed for 3 h. After cooling, ethyl acetate (100 mL) and water (100 mL) were added, the organic layer

was separated, washed with water (3 x 300 mL) and dried ($MgSO_4$). After removal of the solvent, the residue was subjected to column chromatography using CH_2Cl_2/hexane (1:4) as the eluent to give compound **2.25** as white powder (0.49 g, 65%): mp 150-151 °C, ^{1}H NMR δ 7.26-7.49 (m, 10 H), 6.97 (s, 1 H), 6.84 (s, 1 H), 4.12 (t, J = 5.6 Hz, 2 H), 3.03 (t, J = 6.0 Hz, 2H), 2.14-2.17 (m, 2 H), 1.08 (s, 9 H), ^{13}C NMR δ 145.4, 141.0, 135.5, 133.9, 131.4, 130.7, 129.6, 127.9, 127.2, 126.8, 126.3, 126.1, 124.6, 122.1, 117.9, 44.1, 32.1, 31.2, 24.2, 22.4. Anal. calcd for $C_{27}H_{27}N$: C, 88.72; H, 7.45; N, 3.83.

General Procedure for the Preparation of 1-(Benzotriazol-1-yl)-2,3-dihydro-*1H*-pyrrolo[1,2-*a*]indole 2.30 and 1-(Benzotriazol-1-yl)methyl-1,2,3,4-tetrahydro-pyrido[1,2-*a*]indole 2.35. One-pot method

To a solution of 2-(benzotriazol-1-yl)methylindole (**2.27**) (5 mmol) in THF (50 mL) was added a solution of *n*-BuLi (6.25 mL, 10 mmol, 1.6 M in hexane) at -78 °C. The temperature was allowed to warm to -30 °C and the reaction mixture stirred at this temperature for 30 min. After cooling to -78 °C, a solution of 1-chloro-2-bromoethane or 1-chloro-3-bromopropane (5 mmol) in THF (5 mL) was added and the reaction mixture was stirred at -78 °C for a further 3 h. HMPA (2 mL) was added, and the reaction solution was then allowed to warm to room temperature and stirred overnight. Water (100 mL) and ethyl acetate (100 mL) were poured into the reaction mixture, and the organic phase was separated, washed with water (3 x 100 mL) and dried ($MgSO_4$). After removal of the solvent, the crystalline residue was recrystallized from EtOAc/hexane (1:3) to afford the corresponding **2.30** or **2.35**.

1-(Benzotriazol-1-yl)-2,3-dihydro-*1H*-pyrrolo[1,2-*a*]indole 2.30: white plates, 82% yield; mp 164-165 °C; ^{1}H NMR δ 8.02 (d, J = 6.9 Hz, 1 H), 7.56 (d, J = 8.0 Hz, 1 H),

7 37 (d, J = 8.2 Hz, 1 H), 7 21-7.31 (m, 4 H), 7.12 (t, J = 7 6 Hz, 1 H), 6.82 (d, J = 6.7 Hz, 1 H), 6 62 (dd, J = 8 3 Hz, 1 H), 6 28 (s, 1 H), 4 38-4 46 (m, 1 H), 4 18 -4 26 (m, 1 H), 3 21-3 34 (m, 1 H), 2 94-3 04 (m, 1 H), ^{13}C NMR δ 146 4, 138 6, 132 6, 132.5, 131 5, 127 3, 123 9, 121 9, 121 6, 120 0, 110 0, 109 7 95 6, 56 0 42 7, 35 8 Anal calcd for $C_{17}H_{14}N_4$ C, 74 42 H, 5.15, N, 20 43 Found C, 74 50, H, 5.20, N, 20 51

1-(Benzotriazol-1-yl)methyl-1,2,3,4-tetrahydro-pyrido[1,2-*a*]indole 2.35 white needles, 92% yield mp 161–163 °C, ^{1}H NMR δ 8 08 (d, J = 8 5 Hz, 1 H), 7 50 (d, J = 7 8 Hz, 1 H), 7 42 (d, J = 8.1 Hz, 1 H), 7.25-7 34 (m, 3 H), 7 13 (t, J = 7 9 Hz, 1 H), 6 89 (d, J = 8 4 Hz, 1 H), 6.53 (t, J = 7 2 Hz, 1 H), 6.09 (s, 1 H), 4.35-4.17 (m, 2 H), 2 48 2 60 (m, 2 H), 2.21-2.41 (m, 2 H), ^{13}C NMR δ 146 4, 136 4, 132.2, 132 1, 127 7, 127 2, 123 8, 122.0, 120 9, 120 4, 120 2, 110 7, 109 4, 100 8, 55 1, 42 1, 28 8, 21.3 Anal calcd for $C_{18}H_{18}N_4$ C, 74 98, H, 5 59, N, 19 43 Found C 74 92, H, 5.57, N, 19 45

Two step method To a solution of compound **2.27** (2 5 g, 10 1 mmol) in THF (150 mL) was added a solution of *n*-BuLi (12 63 mL, 20.2 mmol, 1 6 M in hexane) at -78 °C, and the temperature was raised to -30 °C The reaction mixture was stirred at this temperature for 30 min and cooled to -78 °C A solution of 1-chloro-3-bromopropane (1 60 g, 10 1 mmol) in THF (10 mL) was added, and the mixture stirred for 3 h at -78 °C The reaction was quenched with saturated NH_4Cl solution, extracted with EtOAc (100 mL), the organic phase separated, washed with water (3 x 100 mL) and dried ($MgSO_4$) After removal of the solvent, the crystalline residue was recrystallized from EtOAc/Hexane (1 4) to give the product **2.34** as white needles (3 02 g, 92 % yield)

mp 136-138 °C, ^{1}H NMR δ 9 36 (s, 1 H), 7 84 (d, J = 8 4 Hz, 1 H), 7 66 (d, J = 7 7 Hz, 1 H), 7 31-7 40 (m, 3 H), 7 11-7.28 (m, 3 H), 6 76 (s, 1 H), 6 23 (t, J = 7 8 Hz, 1 H), 3 53 3 63 (m, 2 H), 2 76-2 85 (m, 2 H), 1 84-1 94 (m, 1 H), 1 69-1 76 (m, 1 H), ^{13}C NMR δ 146 0 136 9, 134 3, 127 7, 127.5 124.3, 122.8, 120 8, 120 2, 119 7, 111 4, 109 9, 101 8, 57 6, 44 0, 31 1, 29 1 Anal. calcd for $C_{18}H_{17}ClN_4$ C, 66 56, H, 5 28, N, 17.25 Found C, 66 22, H, 5.36, N, 17 20

To a solution of compound **2.34** (1 62 g, 5 mmol) in DMSO (20 mL) was added sodium hydride (0 15 g, 5 mmol, 80% in dispersion in mineral oil) at room temperature and the reaction mixture was stirred at this temperature for 12 h Ethyl acetate (50 mL) and water (50 mL) were added, and the organic phase was separated and washed with water (3 x 50 mL) and dried ($MgSO_4$) The solvent was removed under reduced pressure to give the crystalline residue which was recrystallized from EtOAc/hexane (1 3) to afford product **2.35** (1 30 g, 90% yield).

General Procedure for the Reaction of 1-(Benzotriazol-1-yl)-2,3-dihydro-*1H*-pyrrolo[1,2-*a*]indole 2 30 and 1-(Benzotriazol-1-yl)methyl-1,2,3,4-tetrahydropyrido-[1,2-*a*]indole 2.35 with Grignard Reagents

To a solution of **2.30** or **2.35** (2 5 mmol) in toluene (30 mL) under argon was added a solution Grignard reagent (Scheme 1) (5 mmol) in Et_2O (10 mL), and the reaction refluxed for the time indicated in Scheme 3 The solvent was removed under reduced pressure and the residue was extracted with Et_2O (2 x 50 mL) The combined organic solution was washed with water (3 x 50 mL) and dried ($MgSO_4$) After removal of the solvent, the residue was separated by column chromatography using Et_2O/hexane (1 1) as the eluent to give the corresponding product **2.31** or **22.36**.

1-Methyl-2,3-dihydro-*1H*-pyrrolo[1,2-*a*]indole 2.31 white needles, 70% yield. mp 49-50 °C, ^{1}H NMR δ 7.57 (d, J = 7.1 Hz, 1 H), 7.24 (d, J = 7.7 Hz, 1 H), 7.04-7.20 (m, 2 H), 6.16 (s, 1 H), 4.07-4.15 (m, 1 H), 3.92-4.01 (m, 2 H), 3.35-3.42 (m, 1 H), 2.71-2.81 (m, 1 H), 2.12-2.22 (m, 1 H), 1.39 (d, J = 6.9 Hz, 3 H), ^{13}C NMR δ 149.6, 133.0, 132.5, 120.4, 120.2, 119.0, 109.3, 91.4, 43.1, 36.9, 32.1, 19.5. Anal. calcd for $C_{12}H_{13}N$: C, 84.17; H, 7.63; N, 8.18. Found: C, 83.52; H, 7.69; N, 7.94.

1-Phenyl-1,2,3,4-tetrahydropyrido[1,2-*a*]indole 2.36 yellow oil, 58% yield. ^{1}H NMR δ 7.46 (d, J = 7.8 Hz, 1 H), 7.21-7.33 (m, 6 H), 7.16 (t, J = 7.7 Hz, 1 H), 7.06 (t, J = 8.0 Hz, 1 H), 5.92 (s, 1 H), 4.17-4.25 (m, 2 H), 3.94-4.03 (m, 2 H), 2.18-2.23 (m, 2 H), 1.91-2.16 (m, 2 H), ^{13}C NMR δ 144.4, 140.4, 136.3, 128.3, 128.1, 126.6, 120.5, 119.9, 119.7, 108.8, 99.5, 42.4, 42.3, 30.8, 22.2. Anal. calcd for $C_{18}H_{17}N$: C, 87.40; H, 6.93; N, 5.67. Found: C, 87.14; H, 7.35; N, 5.32.

Preparation of 1-(*Trans*-5-Methyl-2-phenyl-1-oxo-2-hexenyl)-2,3-dihydro-*1H*-pyrrolo[1,2-*a*]indole 2.33 To a stirred solution of compound **2.30** (0.82 g, 3 mmol) in THF (100 mL) was added a solution of *n*-BuLi (1.88 mL, 3 mmol) at -78 °C. After 30 min, a solution of 5-methyl-2-phenyl-2-hexenal (0.56 g, 3 mmol) in THF (10 mL) was added and the reaction mixture was allowed to warm to room temperature overnight. The reaction was quenched with saturated NH_4Cl solution (100 mL) and extracted with EtOAc (100 mL). The organic phase was separated, washed with water (3 x 100 mL) and dried over magnesium sulfate. The solvent was removed under reduced pressure and the residue was dissolved in THF (50 mL). To this THF solution was added *p*-toluenesulfonic acid monohydrate (0.57 g, 3 mmol) and the resulting reaction mixture was refluxed for 24 h. After cooling, ethyl acetate (50 mL) and water

(50 mL) were added, the organic layer was separated, washed with water (3 x 50 mL) and dried ($MgSO_4$). The solvent was removed to give an oily residue which was subjected to column chromatography using EtOAc/hexane (1 4) as the eluent to afford the product **2.33** as a white solid (0.54 g, 52 % yield) mp 146-148 °C, ^{1}H NMR δ 7 54 (d, J = 7 8 Hz, 1 H) 7 29-7 40 (m, 3 H), 7 23 (d, J = 8 1 Hz, 1 H), 7 03-7 16 (m, 5 H), 6 18 (s, 1 H), 4 83 (dd, J = 8 2 and 4 4 Hz, 1 H), 4 17-4 26 (m, 1 H), 4 04-4 11 (m, 1 H), 3 07-3 15 (m, 1 H), 2 63-2 69 (m,1 H), 2 12 (t, J =7 1 Hz, 2 H), 1 81-1 90 (m, 1 H), 0 96 (d, J = 6 6 Hz, 6 H), ^{13}C NMR δ 196 8, 144 5, 141 7, 135 8, 133 0, 132 6, 129 7, 128.3, 127 5, 121 0, 120 7, 119 4, 109 6, 94 3, 44 9, 43 4, 38 9, 30 9, 28 6, 22 6, 22 5 Anal calcd for $C_{24}H_{25}NO$ C, 83 93, H, 7.34 N, 4 08 Found C, 83 15, H, 7 52, N, 3 97

Preparation of Fused Indolo[3,2-b]carbazole 2 37 To a solution of compound **2.35** (1 16 g, 4 03 mmol) in CH_2Cl_2 (30 mL) was added $ZnBr_2$ (1 00 g, 4 4 mmol) and the reaction mixture stirred at room temperature for 12 h The reaction solution was filtered. The filtrate was washed with water (3 x 50 mL) and dried ($MgSO_4$). After evaporation of the solvent, the product was separated by column chromatography using CH_2Cl_2/Hexane (1 4) as the eluent to afford product **2.37** as yellow powder (0 67 g, 50% yield) ^{1}H NMR δ 8.24 (d, J = 7 7 Hz, 2 H), 7 40 -7 49 (m, 4 H), 7 20-7 28 (m, 2 H), 4 33 (t, J = 5 2 Hz, 4 H), 3 64 (t, J = 5 4 Hz, 4 H), 2.50-2.54 (m, 4 H), ^{13}C NMR δ 124 8, 122.4, 117 6, 113 8, 40 9, 23 3, 22 6 (Other quaternary carbon signals were not observed due to the poor solubility of the sample in organic solvents) Anal calcd for $C_{34}H_{30}N_2$ C, 85 86 H 5 99, N, 8 33 Found C, 84.27 H, 6 39, N, 8 08

CHAPTER III
GENERAL SYNTHESES OF POLYSUBSTITUTED BENZO[*b*]FURANS

3.1 Introduction

Benzo[*b*]furan derivatives are important because of their occurrence in nature and their physiological properties [75MI337]. Recently there has been a growing interest in developing general and versatile synthetic methods for the synthesis of benzo[*b*]furan derivatives due to their activity as modulators of androgen biosynthesis (furanosteroids), [94JMC4227] as inhibitors of 5-lipoxygenase [94JMC3663], as antagonists of the angiotensin II receptor [94JMC3108], as blood coagulation factor Xa inhibitors [94JMC1200] and as ligands of adenosine A_1 receptor [92JOC7248]. 1-[[4-(Aminoalkyoxy)phenyl]sulfonyl]benzo[*b*]furan derivatives have been synthesized and tested as a potent class of calcium blockers [93JMC1425].

Various methods exist for the synthesis of benzo[*b*]furans [75MI337, 84MI657, 88TL4687], of which the intramolecular cyclization of a suitably substituted benzene is the most often employed [84MI657]. However, recent efforts have centered around the construction of benzo[*b*]furan structures by C-C bond formation using transition metal reagents including copper and especially palladium catalysts [77S122, 80SC699, 86S749, 87TL5291]. Alkyne-based palladium-catalyzed reactions provide some of the most versatile and efficient routes to heterocyclic derivatives [92JCS(CC)41, 96JOC9280]. Thus, Larock and coworkers have reported

the palladium-promoted cyclization of ortho-substituted arylallyl ethers to benzofuran derivatives, and the palladium-catalysed heteroannulation of 1,3-dienes leading to 2,3-dihydrobenzofurans [90JOC3447]

Previous reports in the Katritzky group have demonstrated the use of 1 propargylbenzotriazole as a versatile building blocks for the synthesis of functionalized heterocycles such as 2-(benzotriazol-1-ylmethyl)-pyrroles [95JOC3401] and -indoles [96JOC1624] The anion stabilizing and good leaving abilities of benzotriazolyl moieties in the above ring systems has been utilized in the synthesis of some heterocycles [figure 3 1]

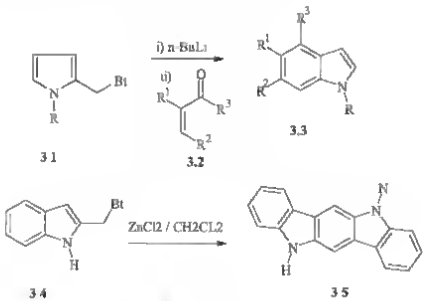


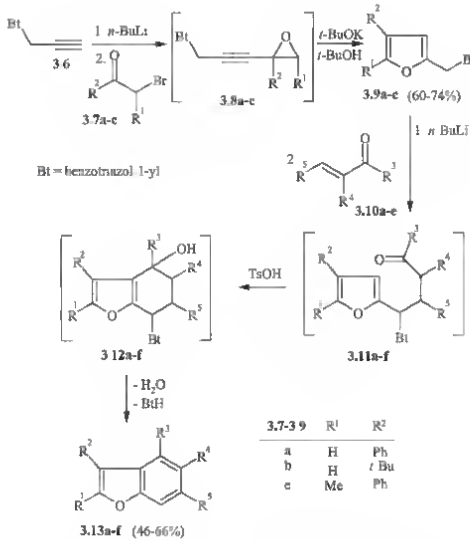
Figure 3 1

These properties of the benzotriazolyl moiety in the above ring systems motivated the extension of this methodology to elaborate furans.

3.2 Results and Discussion

Synthesis of 3,4,5,6-Substituted Benzo[*b*]furans 3.13a-f and 2,3,4,5,6-Substituted Benzo[*b*]furans 3.15a-c

2-(Benzotriazol-1-ylmethyl)furans **3.9a-c** were prepared in one pot from alkynyloxiranes **3.8a-c**, themselves derived from 1-propargylbenzotriazole (**3.6**) and α-bromo ketones **3.7a-c** [95JOC638]. Refluxing **3.8** in DMF in the presence of other bases such as aniline or potassium carbonate failed to give the desired product **3.9**. The use of sodium hydride gave very low yield, better yields were obtained with *t*-BuOK and *t*-BuOH. Treatment of **3.9a-c** with 1 equiv of *n*-BuLi at -78 °C, followed by 1 equiv of α,β-unsaturated ketones or aldehydes **3.10a-c** gave 1,4-addition intermediates **3.11a-f**. To confirm the structure of these intermediates, **3.11a** was isolated, purified and characterized by NMR spectroscopy. There was no formation of the 1,2-addition product observed. Subsequently, intermediates **3.11a-f** (obtained as mixtures of diastereomers), without further purification, were treated with *p*-toluenesulfonic acid in 1,4-dioxane under reflux to undergo intramolecular cyclization to intermediates **3.12a-f**, followed by spontaneous elimination of benzotriazole and water to give the benzo[*b*]furans **3.13a-f** (figure 3.2). It was found that the best solvent was 1,4-dioxane, initial attempts to carry out these cyclization reactions in THF failed, probably due to the lower boiling temperature of THF.



3.7-3.9	R^1	R^2
a	H	Ph
b	H	*t* Bu
c	Me	Ph

3.10	R^3	R^4	R^5
a	Ph	H	Ph
b	H	Me	Ph
c	Me	H	Ph
d	H	H	Me
e	E	H	Me

3.11, 3.12, 3.13	R^1	R^2	R^3	R^4	R^5
a	H	Ph	Ph	H	Ph
b	H	Ph	Me	H	Ph
c	H	*t* Bu	H	Me	Ph
d	Me	Ph	Ph	H	Ph
e	H	*t* Bu	Me	H	Ph
f	H	t-Bu	H	H	Me

Figure 3.2

Alternatively, the 2-(benzotriazol-1-yl)methyl moiety was alkylated by lithiation of **3.9a-c** with 1 equiv of *n*-BuLi at −78 °C for 30 min, followed by reactions with *n*-butyl iodide or benzyl bromide as electrophiles for 12 h to give **3.14a-c** in good yields. Reactions of **3.14a-c** with α,β unsaturated ketones followed by cyclization gave polysubstituted benzo[*b*]furans **3.15a-c**

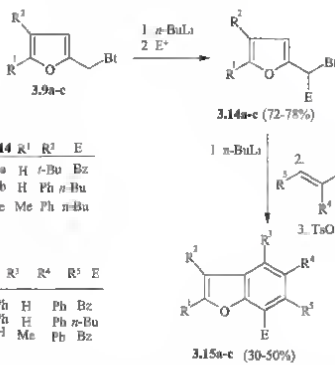


Figure 3.3

The reaction of **3.14a** with α-methylcinnamaldehyde gave a very low yield of **3.15c** (30 %) and about 50 % of the alkene **3.17** (figure 3.4) The reaction was then repeated and the intermediate isolated and found to be the 1,2 addition product **3.16** The intermediate then underwent dehydration in the presence of acid with subsequent elimination of benzotriazole to give the desired product **3.15c** The alkene **3.17** may

have been formed by the deprotonation of the benzylic proton followed by the loss of benzotriazole This was similar to the formation of **3 24** in which the dehydrobenzotriazolylation was effected by *t*-BuOK (Scheme 3 5) The formation of **3.17** occurs faster than **3 15c**, hence, lower yield of the desired product

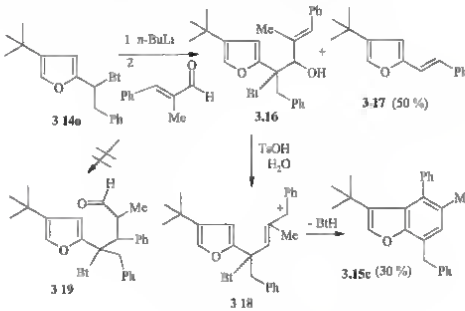


Figure 3 4

Synthesis of 2-(Benzotriazol-1-ylmethyl)benzo[*b*]furan (3 22) and Synthetic Manipulation of the Benzotriazol-1-ylmethyl Attached Side Chain

The synthesis of 2-substituted benzo[*b*]furans *via* palladium catalyzed heteroannulation of acetylenic compounds has been reported [92JCS(CC)41]. The presence of a benzotriazolyl group at the 2-position of the benzo[*b*]furan ring should allow further elaboration to generate various products by sequential lithiation, alkylation and elimination or substitution of the benzotriazolyl group

When a mixture of *ortho*-iodophenol (**3.20**) and 1-propargylbenzotriazole (**3.6**) were heated in the presence of $(PPh_3)_2PdCl_2$, CuI and Et_3N at 60 °C using DMF as solvent, 2 (benzotriazol-1-yl)methylbenzofuran (**3.22**) was obtained in 70% yield after 12 h. The yield was reduced when higher temperature was employed, due to decomposition of starting material. The catalyst $(PPh_3)_2PdCl_2$ was found to give better yields, use of other catalyst such as Pd(OAc) gave very low yields. The catalyst was readily prepared from the reaction of palladium chloride with sodium chloride and subsequent reaction of the tetrachloride with triphenylphosphine in ethanol. Lithiation of **3.22** with 1 equiv of *n*-BuLi followed by alkylation with electrophiles gave **3.23a-c** in good yields. When **3.23a** was refluxed in a 1:1 mixture of *t*-BuOH/THF in the presence of *t*-BuOK for 24 h, 2-[*trans*-(2-phenyl)ethenyl]benzofuran **3.24** was exclusively formed in excellent yield. No formation of the *cis*-isomer was observed by NMR or GCMS.

Recently, Katritzky and co-workers found that stereoselective olefination of aldehydes and ketones with *N*-benzyl- and *N*-allyl benzotriazoles was promoted by low-valent titanium [97JOC238]. In the present study this method was applied to 2-(benzotriazol-1-ylmethyl)benzofuran (**3.22**). Thus, compound **3.22** was treated with 1 equiv of *n*-BuLi followed by the reaction with trimethylacetaldehyde to give a mixture of distereomers **3.23c**, which upon treatment with low-valent titanium, underwent dehydroxybenzotriazolation stereospecifically to give *trans*-1-(benzofuran-2-yl)-2-(*t*-butyl)ethlene (**3.26**) exclusively. The *trans*-structure was confirmed by the large coupling constant (16.2 Hz) of the double bond protons.

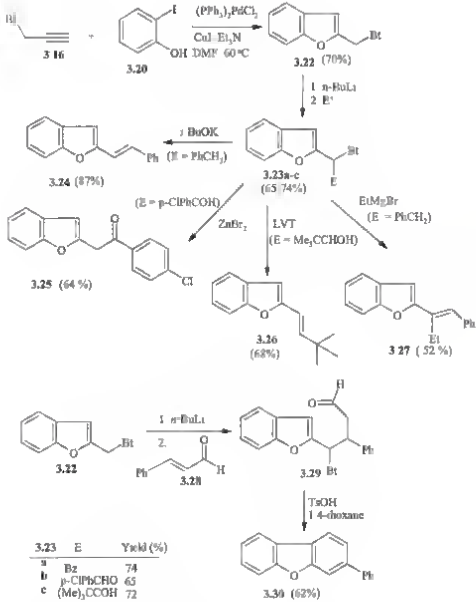


Figure 3 5

Surprisingly, nucleophilic substitution of the benzotriazole group in **3.23a** with Grignard reagent was followed by dehydrogenation to give the alkene **3.27**. When refluxed with 2 equivalent of Grignard reagent, **3 23a** was unchanged after 24h.

When 5 equivalents of Grignard reagent was used, product **3.27** was obtained. The excess Grignard reagent acted as a strong base, deprotonating the benzylic proton followed by loss of the benzotriazolyl group (as observed in the formation of **3.17** and **3.24**). Subsequent substitution of the alkenyl proton with the excess Grignard gave **3.27**. Intermediate **3.23b** when treated with zinc bromide in THF under reflux, remained unchanged after 24 h. When THF was distilled off and the product heated neat at 150 °C, it underwent a pinacol type reaction with elimination of benzotriazole to give the ketone **3.25** [95JACS12015, 96JOC7571]. Lithiation of **3.22** with 1 equiv of *n*-BuLi, followed by addition of α,β-unsaturated aldehyde (**3.28**) gave the 1,4-addition product **3.29**, which, without further purification, was refluxed in 1,4-dioxane in the presence of *p*-toluenesulfonic acid to give dibenzofuran **3.30** in good yield.

In conclusion, taking advantage of the electron withdrawing and donating properties of benzotriazole, general syntheses of polysubstituted benzo[*b*]furans have been described. These approaches utilized readily available starting materials under relatively mild conditions, and involved sequential lithiation and alkylation of the 2-(benzotriazol-1-yl)methyl side chain of furans **3.9a-c**, **3.14a-c** and benzo[*b*]furan **3.22** with α,β-unsaturated ketones or aldehydes, followed by intramolecular cyclization with elimination of benzotriazole and water to give **3.13a-f**, **3.15a-c** and **3.30**. The good leaving ability of benzotriazole in **3.23** enabled synthesis of 2-functionalized benzofurans by base assisted elimination of benzotriazole to give **3.24**, Lewis acid assisted elimination of benzotriazole to give **3.25** and low valent titanium promoted olefination to give **3.26**.

3.3 Experimental

Melting points were determined on a hot-stage microscope and are uncorrected. ^{1}H NMR spectra were recorded on a 300 MHz spectrometer using TMS as the internal standard and $CDCl_3$ as the solvent ^{13}C NMR spectra were recorded at 75 MHz on the same instrument with the solvent peak ($CDCl_3$) as the reference. HRMS and elemental analyses (C,H,N) were carried out within the department. Dichlorobis(triphenylphosphine)palladium(II) was freshly prepared according to literature procedure [81JOC4439] 1-Propargylbenzotriazole **(3.6)** [92LA843] and 2-(benzotriazol-1-ylmethyl)furan **(3.9a)** were prepared according to previously reported procedures and compounds **3.9b-e** were prepared using the same procedure [95JOC638]

2-(Benzotriazol-1-ylmethyl)-4-(*t*-butyl)furan (3.9b) white micro crystals, yield 74% mp 63-65 °C, ^{1}H NMR δ 8.06 (d, J = 8.1 Hz, 1 H), 7.59 (d J =8.4 Hz, 1 H), 7.48 (t, J = 7.7 Hz, 1 H), 7.37 (t, J = 7.7 Hz, 1 H), 7.12 (s, 1 H), 6.39 (s, 1 H) 5.77 (s, 2 H), 1.54 (s, 9 H), ^{13}C NMR δ 147.8, 146.1, 137.3, 137.2, 132.8, 127.4, 123.8, 119.8, 109.8, 109.2, 45.2, 30.6, 29.8 Anal. Calcd for $C_{15}H_{17}N_3O$ C, 70.56, H, 6.71, N, 16.46 Found. C, 70.62, H, 7.07, N, 16.58

2-(Benzotriazol-1-ylmethyl)-4-phenyl-5-methylfuran (3.9c) yellow micro crystals, yield 60% mp 109-110 °C. H NMR δ 8.04 (d, J = 8.4 Hz, 1 H), 7.62 (d, J = 8.2 Hz, 1 H), 7.45 (t, J = 7.3 Hz, 1 H), 7.38-7.21 (m, 6 H) 6.56 (s, 1 H), 5.78 (s, 2 H), 2.36 (s, 3 H), ^{13}C NMR δ 148.7, 146.3, 145.5, 133.4, 132.9, 128.6, 127.4, 126.6, 123.8, 123.9,

122 1, 120 0, 111 2, 109 8 45.2, 13 0 Anal Calcd for $C_{19}H_{15}N_3O$ C, 74 72, H, 5.23, N, 14 52 Found C, 74 94, H, 5.27, N, 14 67

Preparation of 2-(Benzotriazol-1-ylmethyl)benzo[*b*]furan (3.22) A mixture of *ortho*-iodophenol (5 50 g, 25 mmol), $(PPh_3)_2PdCl_2$ (0 61 g, 0 88 mmol), CuI (0 62 g, 3 25 mmol) and triethylamine (5 06 g, 50 mmol) were stirred in DMF (60 mL) under nitrogen for 1 h. 1-Propargylbenzotriazole (**3.1**) (7 90 g, 50 mmol) was added and the mixture stirred at room temperature for an additional 1 hour and then heated at 60 °C for 16 h. The mixture was then cooled, poured into water (150 mL) and extracted with CH_2Cl_2 (3 x 50 mL) The combined extracts were washed with NaOH (5 N, 3 x 100 mL) followed by water (3 x 100 mL) and dried ($MgSO_4$) After evaporation of the solvent, the residue was purified by column chromatography using EtOAc/Hexane (1 3) to give the product 3 22 as brown needles, yield 70% mp 160-162 °C; ^1H NMR δ 8 03 (d, J = 8 5 Hz, 1 H), 7 91 (d, J = 8 5 Hz, 1 H) 7 62 7 52 (m, 2 H), 7 49-7 37 (m, 2 H), 7.30-7 18 (m, 2 H) 7 05 (s, 1 H), 6 20 (s, 2 H), ^{13}C NMR δ 154 4, 151 0 145 2, 132 6, 127 4, 127.3, 124 5, 123 8, 122 8, 121 1 119.1, 110 9, 110 3, 106 1 44 6 Anal Calcd for $C_{15}H_{11}N_3O$ C, 72 28 H, 4 45, N, 16 86 Found C, 72.12, H, 4 42, N, 16 70

General Procedure for the Preparation of 3.14a-c and 3.23a-c *via* the Alkylation of 2-[(Benzotriazol-1-ylmethyl)]-furans 3 9a-c and -benzofuran (3 22)

To a solution of 2-[(benzotriazol-1-ylmethyl)]-furan **3.9a-c** or -benzofuran (**3 22**) (15 7 mmol) in THF (100 mL) was added a solution of *n*-BuLi (15 7 mmol 9 8 mL, 1 6 M in hexane) at -78 °C After 30 min, a solution of the electrophile (benzyl bromide, *n*-butyl iodide, benzaldehyde or *t*-butylacetaldehyde) (15 7 mmol) in THF

(10 mL) was added The reaction mixture was stirred at this temperature for 4 h and allowed to warm to room temperature overnight The reaction was quenched with saturated NH_4Cl solution (50 mL), extracted with EtOAc, washed with brine (3 x 50 mL) and dried ($MgSO_4$) The solvent was removed to give the crude product which was purified by column chromatography to give the corresponding compounds **3 14a-e** or **3 23a** The crude products **3 23b,c** were used directly for the synthesis of compounds **3.25** and **3.26** without further purification and the yields were determined by GCMS

2-[1-(Benzotriazol-1-yl)-2-phenylJethyl-4-(*t*-butyl)furan (3.14a) purified by column chromatography using EtOAc/hexane (1 1), white powder, yield 78%. mp 104-105 °C; ^1H NMR δ 8 01 (d, J = 8 1 Hz, 1 H), 7.45-7.26 (m, 3 H), 7 12 (d, J = 6 0 Hz, 4 H), 6 99-6 93 (m, 2 H), 6.35 (s, 1 H), 6 13 (t, J = 7 3 Hz, 1 H), 3 90-3 70 (m, 2 H), 1 18 (s, 9 H), ^{13}C NMR δ 150 6, 146 1, 137 2, 136 8 136 3 132 6, 128 8, 128.5, 127 1, 126 9, 123 7, 119 9, 109 9, 108 3, 59 2, 38 8, 30 7, 29 8 Anal Calcd for $C_{28}H_{23}N_3O$ C, 76 49, H, 6 71, N, 12 16 Found C, 76 65, H, 6 93, N, 12.27

2-[1-(Benzotriazol-1-yl)]pentyl-4-phenylfuran (3.14b) purified by column chromatography using EtOAc/hexane (1 1), white powder, yield 76% mp 113-115 °C, ^1H NMR δ 8 08 (d, J = 8 1 Hz, 1 H), 7 64 (s, 1 H), 7 55 (d, J = 8 1 Hz, 1 H), 7 45 -7 23 (m, 7 H), 6 72 (s, 1 H), 6 07 (t, J = 7 5 Hz, 1 H), 2 61-2 52 (m, 2 H), 1 44-1 17 (m, 4 H), 0 87 (t, J = 7 1 Hz, 3 H), ^{13}C NMR δ 152.5, 146 4, 138.2, 132.2, 131 7, 128 8, 128 7, 127 3, 127 2, 125 7, 123 8, 120 1, 110 1 107.5, 57 7, 31 9, 28 1, 22 0, 13 7 Anal Calcd for $C_{21}H_{21}N_3O$ C, 76 11, H, 6 39, N, 12 68 Found C, 75 80, H, 6.55, N, 12 54

2-[1-(Benzotriazol-1-yl)]pentyl-4-phenyl-5-methylfuran (3.14e) purified by column chromatography using EtOAc/hexane (1:1), white powder, yield 72%, mp 110-111 °C, ^{1}H NMR δ 8.08 (d, J = 8.1 Hz, 1 H), 7.59 (d, J = 8.1 Hz, 1 H), 7.46-7.23 (m, 7 H), 6.54 (s, 1 H), 6.03 (t, J = 7.8 Hz, 1 H), 2.59-2.52 (m, 2 H), 2.37 (s, 3 H), 1.43-1.17 (m, 4 H), 0.87 (t, J = 6.9 Hz, 3 H), ^{13}C NMR δ 149.0, 148.1, 146.4, 133.5, 132.2, 128.6, 127.4, 127.1, 126.6, 123.8, 121.7, 120.1, 110.3, 109.7, 57.8, 31.8, 28.3, 22.1, 13.8, 13.1. Anal. Calcd for $C_{22}H_{23}N_3O$: C, 76.49; H, 6.71; N, 12.16. Found: C, 76.57; H, 6.85; N, 12.19.

2-[1-(Benzotriazol-1-yl)-2-phenyl]ethylbenzo[*b*]furan (3.23a) purified by column chromatography using EtOAc/hexane (1:1), white powder, yield 74%, mp 134-135 °C, ^{1}H NMR δ 8.03 (d, J = 8.0 Hz, 1 H), 7.53-7.21 (m, 8 H), 7.18-7.04 (m, 4 H), 6.74 (s, 1 H), 6.33 (t, J = 7.7 Hz, 1 H), 3.95 (d, J = 7.7 Hz, 2 H), ^{13}C NMR δ 153.3, 146.2, 144.8, 136.1, 132.7, 128.8, 128.6, 127.7, 127.4, 127.1, 124.9, 123.9, 123.2, 121.3, 120.1, 111.4, 109.8, 105.5, 59.4, 38.7. Anal. Calcd for $C_{24}H_{17}N_3O$: C, 77.86; H, 5.05; N, 12.38. Found: C, 77.86; H, 5.07; N, 12.43.

General Procedure for the Preparation of PolySubstituted Benzo[*b*]furans 3.13 a-f, 3.15a-c and 3-Phenyldibenzo[*b*]furan (3.30)

To a solution of compound **3.9** or **3.14** or **3.22** (7.3 mmol) in THF (100 mL) was added a solution of *n*-BuLi (7.3 mmol, 4.6 mL, 1.6 M in hexane) at -78 °C, the solution was stirred at this temperature for 30 min. A solution of an appropriate α,β-unsaturated ketone or aldehyde (**3.10** or **3.28**) (7.3 mmol) in THF (10 mL) was added and the reaction mixture was stirred at -78 °C for 20 h. A saturated NH_4Cl solution (100 mL) was added and the solution was extracted with EtOAc (100 mL). The

organic phase was separated, washed with saturated NH_4Cl solution (3 x 100 mL) and dried ($MgSO_4$) After removal of the solvent, the residue was dissolved in 1,4-dioxane (50 mL) *p*-toluenesulfonic acid (2.8 g, 14 6 mmol) added and the solution was refluxed for 24 h. The mixture was cooled, diluted with water (50 mL) and extracted with Et_2O (3 x 50 mL) The combined extracts were washed with water (3 x 50 mL) and dried ($MgSO_4$) The solvent was removed and the residue was subjected to column chromatography or recrystallization to afford the corresponding product **3.13a-f** or **3.15a-c** or **3.30**

3,4,6-Triphenylbenzo[*b*]furan (3 13a) purified by recrystallization from pentane, white micro crystals, yield 53% mp 108-109 °C, ^{1}H NMR δ 7 75 (s, 1 H), 7 69 (d, *J* = 7 4 Hz, 2 H), 7 46-7 32 (m, 5 H), 7 07-6 91 (m, 10 H), ^{13}C NMR δ 156 8, 143 1, 141 0, 139.3, 138.2, 136 8 132.0, 129 4, 129 1, 128 9, 127.5, 127 4, 127 3, 126 8, 126 6, 124 0, 123 3, 109 0 Anal Calcd for $C_{28}H_{18}O$ C, 90 14, H 5 24 Found C, 90 09 H, 5 48

4-Methyl-3,6-diphenylbenzo[*b*]furan (3 13b) purified by column chromatography using CH_2Cl_2/hexane (1 4) as the eluent, white crystals, yield 50% mp 119-121 °C, ^{1}H NMR δ 7 62 7 48 (m, 3 H), 7.54 (s, 1 H), 7 46-7.26 (m, 9 H), 2 30 (s, 3 H), ^{13}C NMR δ 142 4, 141.2, 138 1, 132 8, 132 1, 130 1, 128 8, 128 0, 127 6, 127 4, 127.3, 127 1, 125 1, 124 0 123.3, 107 8, 19 9 Anal Calcd for $C_{21}H_{16}O$ C, 88 70, H, 5 67 Found C, 88 37, H, 5 94

3-(*t*-Butyl)-5-methyl-6-phenylbenzo[*b*]furan (3 13c) purified by column chromatography using CH_2Cl_2/hexane (1 4) as the eluent, yellow crystals, yield 52% mp 54-55 °C, ^{1}H NMR δ 7 63 (d, *J* = 7 2 Hz, 2 H), 7.54 (s, 1 H), 7 45 7 40 (m, 3 H),

7 35-7.30 (m, 2 H), 2 84 (s, 3 H) 1 47 (s 9 H), ^{13}C NMR δ 157 8, 141 0, 137 3, 131 0, 130 8, 128 7, 127 2, 127 1 125 4, 124 7, 107 9, 31 5, 30 4, 24.2 Anal. Calcd for $C_{19}H_{20}O$ C, 86.32, H, 7 63 Found C, 86 60 H, 7 94

2-Methyl-3,4,6-triphenylbenzo[*b*]furan (3 13d) purified by column chromatography using CH_2Cl_2/hexane (1 4) as the eluent, white crystals, yield 46% mp 102-103 °C ^{1}H NMR δ 7 69-7 66 (m, 3 H), 7 45-7 40 (m, 3 H), 7 32 (t, *J* = 7.2 Hz, 1 H), 7 07-6 88 (m, 8 H), 6 87 (d *J* = 7 8 Hz, 2 H), 2.42 (s, 3 H), ^{13}C NMR δ 155 1, 152.8, 141.2, 139 1, 136 9, 135 8, 133 1, 129 8, 129.2, 128 8, 127 4, 127.3, 127 2, 127 1, 126 4, 126 2, 125.2, 123 7, 117 6, 108 1, 12.6. Anal. Calcd for $C_{27}H_{20}O$ C, 89 97 H, 5 59 Found. C, 89 69, H, 5 70

3-(*t*-Butyl)-4-methyl-6-phenylbenzo[*b*]furan (3 13e) purified by column chromatography using CH_2Cl_2/hexane (1 4) as the eluent, yellow crystals, yield 48% mp 55-57 °C, ^{1}H NMR δ 7 56 (d, *J* = 7 5 Hz, 2 H), 7 40 (s, 1 H), 7.36-7.33 (m, 3 H), 7 27 7 23 (m 2 H), 2 77 (s, 3 H), 1 41 (s 9 H), ^{13}C NMR δ 157 8, 141 0, 140 9, 137 3, 131 0, 130 8, 128 7, 127.2, 127 1, 125.4 124 8, 107 9, 31 6 30 5, 24 2 Anal Calcd for $C_{19}H_{20}O$ C 86 32, H, 7 63 Found C, 86 60, H, 7 94

3-(*t*-Butyl)-6-methylbenzo[*b*]furan (3 13f) purified by column chromatography using CH_2Cl_2/hexane (1 4) as the eluent, yellow oil, yield 40% ^{1}H NMR δ 7 50 (d, *J* = 8 0 Hz, 1 H), 7 17 (s, 2 H), 6.95 (d, *J* = 8 0 Hz, 1 H), 2.36 (s, 3 H), 1.31 (s, 9 H), ^{13}C NMR δ 156 5, 138 7, 133 9, 130.2, 124.4, 123 3, 121 1, 111 9, 30 0, 29 7, 29 4 HRMS calcd for $C_{13}H_{16}$ 188 1201, found 188 1203

3-(*t*-Butyl)-4,6-diphenyl-7-benzylbenzo[*b*]furan (3 15u) purified by column chromatography using CH_2Cl_2/hexane (1 4) as the eluent, white crystals, yield 50%

mp 148-149 °C, ^{1}H NMR δ 7 43 (s 3 H), 7.35-7.30 (m, 8 H), 7.20-7 05 (m, 5 H), 6 98 (s, 1 H) 4 31 (s, 2 H), 1 05 (s, 9 H) ^{13}C NMR δ 155 7, 143 8, 141 5, 141 0, 140 7, 137 1, 134 7, 131.2, 130.5, 129 7, 128 4, 128.1, 128 0 127 9, 127 4, 127 3, 126 9, 125 7, 124 4 121 0, 32.7, 31 0, 30 5 Anal Calcd for $C_3H_{28}O$ C, 89 38, H, 6 78 Found C, 89 37, H, 6 96

2-Methyl-3,4,6-triphenyl-7-butylbenzo[*b*]furan (3 15b) purified by column chromatography using CH_2Cl_2/hexane (1 4) as the eluent, white crystals, yield 66% mp 95-96 °C, ^{1}H NMR δ 7 44-7.33 (m 5 H), 7 12-6 92 (m, 11 H), 2 96 (t, J = 8 0 Hz, 2 H), 2 48 (s, 3 H), 1 72-1 64 (m, 2 H), 1 39-1 30 (m, 2 H) 0 88 (t, J = 7 3 Hz, 3H), ^{13}C NMR δ 153 6, 152 2, 141 7, 139.2, 137 2, 133 4, 132.6, 129 9, 129 7, 129 3 128 0, 127 4, 127 1, 126 9, 126 7, 126.5, 126 1, 124.6, 122 9, 117 8, 32.4, 26 7, 22.9, 13 8, 12 7 Anal Calcd for $C_{31}H_{28}O$ C, 89.38, H, 6 78 Found. C, 89 06, H, 7 18

3-(*t*-Butyl)-5-methyl-6-phenyl-7-benzylbenzo[*b*]furan (3.15c). purified by column chromatography using CH_2Cl_2/hexane (1 4) as the eluent, yellow oil, yield 30%, ^{1}H NMR δ 7 41 (s, 1 H), 7 25-7 22 (m, 4 H) 6 99-6 94 (m, 5 H), 6 80 (d, J = 6.0 Hz, 2 H), 3 92 (s, 2 H), 2 01 (s 3 H) 1 34 (s, 9 H), ^{13}C NMR δ 153 8, 140 7, 140.1, 139 5, 137 9, 130 3, 130 1, 129 9, 128.6, 128 1, 127 9, 126 8, 125 6, 125.5, 122.7, 120.2 33 2, 31 0, 30 0, 21 7 Anal Calcd for $C_{26}H_{26}O$ C, 88 09, H, 7 39 Found C, 87 67, H, 7 56

3-Phenyldibenzo[*b*]furan (3.30) purified by column chromatography using CH_2Cl_2/hexane (1 4) as the eluent, white crystals, yield 62% mp 128-130 °C, ^{1}H NMR δ 7 93-7 89 (m, 2 H), 7 74 (s, 1 H), 7 64 (d, J = 7 4 Hz, 2 H), 7.54 (d, J = 7 7 Hz, 2 H), 7 46-7.28 (m, 5 H), ^{12}C NMR δ 156 9, 156 7 141 1, 140 8, 128 9, 127 5,

127.4, 127.1, 124.1, 123.3, 122.8, 122.1, 120.7, 120.6, 111.7, 110.1. Anal. Calcd for $C_{18}H_{12}O$: C, 88.50; H, 4.95. Found: C, 88.31; H, 4.94.

Preparation of 2-[*trans*-(2-Phenyl)ethenyl]benzo[*b*]furan (3.24)

2-[1-(Benzotriazol-1-yl)-2-phenyl]ethylbenzo[*b*]furan (**3.23a**) (1.0 g, 2.95 mmol) and *t*-BuOK (0.66 g, 5.90 mmol) were dissolved in a mixture of dry THF (20 mL) and *t*-BuOH (30 mL). The mixture was refluxed for 24 h. After cooling, the reaction was quenched with water (100 mL) and extracted with Et_2O (3 x 100 mL). The combined extracts were washed with water (3 x 100 mL) and dried ($MgSO_4$). Evaporation of the solvent followed by column chromatography using CH_2Cl_2/Hexane (1:4) as the eluent, gave the product as white crystals, yield 87%, mp 125-126 °C, ^{1}H NMR δ 7.47 (t, J = 8.9 Hz, 4 H), 7.35-7.17 (m, 6 H), 6.95 (d, J = 16.2 Hz, 1 H), 6.61 (s, 1 H); ^{13}C NMR δ 155.1, 154.9, 136.6, 130.3, 129.1, 128.7, 128.1, 126.7, 124.6, 122.8, 120.8, 116.4, 110.9, 105.1. Anal. Calcd for $C_{18}H_{12}O$: C, 87.25; H, 5.49. Found: C, 87.11; H, 5.57.

Preparation of 2-[*trans*-2-(*t*-Butyl)ethenyl]benzo[*b*]furan (3.26)

To a solution of 2-[(benzotriazol-1-yl)methyl]benzo[*b*]furan (**3.22**) (2.0 g, 8.03 mmol) in THF (80 mL), under argon was added a solution of *n*-BuLi (5.02 mL, 8.03 mmol, 1.6 M in hexane) at -78 °C. The mixture was stirred at -78 °C for 1 h and a solution of *t*-butylacetaldehyde (0.7 g, 8.03 mmol) in THF (10 mL) was added. After being stirred for 2 h at -78 °C, the reaction was quenched with saturated NH_4Cl solution (100 mL) and extracted with diethyl ether (100 mL). The organic phase was separated, washed with brine (3 x 100 mL) and dried ($MgSO_4$). The solvent was

removed under reduced pressure to give the crude product **3.23e** which was used in the following reaction without further purification.

A mixture of $TiCl_3$ (3.85 g, 25 mmol) and zinc dust (5.4 g, 82.7 mmol) in dry DME (100 mL) was refluxed for 1 h under argon. After cooling, the above crude compound **3.23e** in dry DME (10 mL) was added and refluxed for 12 h. The reaction mixture was cooled, diluted with diethyl ether (100 mL) and filtered. The filtrate was washed with NaOH (5%, 3 x 100 mL) and brine (3 x 100 mL), and dried ($MgSO_4$). After removal of the solvent, the residue was purified by short column chromatography using hexane as the eluent to give the product as an oil, yield 68%. ^{1}H NMR δ 7.47-7.39 (m, 2 H), 7.20-7.14 (m, 2 H), 6.53 (d, J = 16.2 Hz, 1 H), 6.44 (s, 1 H), 6.23 (d, J = 16.2 Hz, 1 H), 1.13 (s, 9 H). ^{13}C NMR δ 155.5, 154.6, 144.2, 129.2, 123.9, 122.6, 120.5, 114.0, 110.7, 102.9, 33.5, 29.4. Anal. Calcd for $C_{14}H_{16}O$: C, 83.96; H, 8.05. Found: C, 84.07; H, 8.38.

Preparation of 1-[4-Chlorophenyl)-2-(benzofuran-2-yl)ethanone (3.25)

To a solution of 2-[(benzotriazol-1-ylmethyl)]benzo[*b*]furan (**3.22**) (1.0 g, 4 mmol) in THF (50 mL) at –78 °C under argon was added *n*-BuLi (1.6 M, 2.74 mL, 4.4 mmol). After 30 min, a solution of 4-chlorobenzaldehyde (0.62 g, 4.4 mmol) in THF (10 mL) was added. The mixture was kept at -78 °C for 4 h and allowed to warm to room temperature overnight. A solution of zinc bromide (15 mmol) in THF (15 mL) was added. THF was removed and the residue was heated at 150 °C for 12 h. Ethyl acetate (100 mL) and diethyl ether (100 mL) were added and the mixture stirred for 1 h at room temperature. The solid was filtered off, and the solution was washed with water (2 x 100 mL) and dried ($MgSO_4$). The solvent was removed and the residue

was subjected to column chromatography (EtOAc/hexane, 1 7) to give the product as yellow crystals, yield 64%, mp 105-106 °C, ^{1}H NMR δ 7 96 (d, J = 8 3 Hz, 2 H), 7 50 (d, J = 8 2 Hz, 1 H), 7 42 (d, J = 8 4 Hz, 3 H), 7 23 7 18 (m, 2 H), 6 62 (s, 1 H), 4 39 (s, 2 H), ^{13}C NMR δ 193 1, 154 9, 151 0, 140 0, 134 5, 130 0, 129 1, 129 0, 123 9, 122.8, 120 7, 111 0, 105 5, 38 8 Anal Calcd for $C_{16}H_{11}O_2Cl$ C, 70 99, H, 4 10 Found C, 70 93, H, 4 00

Preparation of 2-[1-Ethyl-2-phenyl]ethenyl]benzofuran (3.27)

To a solution of compound **3.23a** (2 mmol) in toluene (30 mL) under argon was added a solution of ethylmagnesiumbromide (4 mmol) in Et_2O, and the reaction mixture was refluxed for 3 h. The solvent was removed under reduced pressure and the residue was extracted with Et_2O (2 x 50 mL) The combined diethyl ether solution was washed with water (2 x 50 mL) and dried ($MgSO_4$) After removal of the solvent, the residue was purified by column chromatography using CH_2Cl_2/hexane (1 4) as the eluent to give the product as yellow powder 52% yield, mp 63-64 °C, ^{1}H NMR δ 7 79 (d, J = 7 4 Hz, 2 H), 7 36 (t, J = 7 8 Hz, 2 H), 7 18 (t, J = 7 2 Hz, 2 H), 7 09-7 05 (m, 2 H), 6 97 (t, J = 7 4 Hz, 1 H), 6 44 (s, 1 H) 5.59 (s, 1 H) 2 40 (q, J = 7 1 Hz, 2 H), 1 28 (t, J = 7.4 Hz, 3 H), ^{13}C NMR δ 152 3, 149 7, 136 1, 134.7, 128 7 128 3, 128 2, 125 9, 125.6, 122.5, 121 6, 121 4, 114 7, 101.6, 24.7, 12.2. Anal. Calcd for $C_{18}H_{16}O$ C, 87 06, H, 6 49 Found C, 87 24, H, 6.60

CHAPTER IV
1-(AZIDOMETHYL)-BENZOTRIAZOLE AND -5-PHENYL-1,2,3, 4-TETRAZOLE AS 1,3-DIPOLAR CYCLOADDITION COMPONENTS

4 1 Introduction

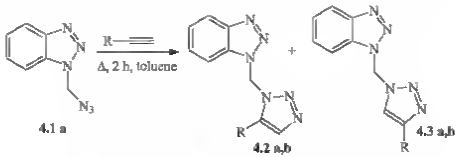
The general route to triazoline synthesis involves the 1,3-dipolar cycloaddition of azides to olefins [67T349] First reported in 1912 [12LA23] this method has subsequently been extended to various substituted and strained olefins The mechanism of the addition has been reported to occur in a concerted manner generating an unsymmetrical intermediate [65JACS306] The rate of the reaction is therefore affected by the electronic nature of substituents on both the olefin and the azide.

Studies have revealed a positive ρ value for the addition of substituted phenyl azides to norbornene [65JACS306], supporting a polar transition state Enol ethers and enamines show high reactivity towards azides [64JACS2213, 65CB1138], indicating a resonance interaction between the adjacent heteroatom and the partial positive charge generated in the transition state Generally, substituents capable of stabilizing the positive charge in the transition state, and hence lowering the activation energy should also facilitate the reaction rate Electron withdrawing groups on the azide accelerate the reaction The rate of the reaction also increases with

increase in ring strain of the olefin [84M1559] Carbon-carbon double bonds that are not strained and are not activated react very slowly with azides.

The cycloaddition reactions of alkyl and aryl azides are well investigated [84M1559] Their reactions with alkynes give mixtures of isomeric 1,2,3-triazoles, whereas those with alkenes proceed regioselectively to form single1,2,3 -triazolines In some cases aziridines or enamines are produced by subsequent 1,2,3 -triazoline ring transformation Cycloadditions to azido groups attached to carbon atoms of a heterocycle directly, or through a methylene group(s) are of recent interest due to their application in the synthesis of compounds of biological activity 2-Azidobenzo [*b*]thiophenes underwent thermolysis in the presence of alkenes to give aziridines and/or 4-cyanoisochromans [88JCS(P1)3375, 90JCS(P1)2971] In reactions with alkyl acrylates, 6-azidobenzothiazoles formed 1,2,3-triazolines, which were cleaved in the presence of bases to give diazopropanoic acid esters [82CH638]. Similarly, 2- and 4-azidopyrimidines reacted with acetylacetone to yield pyrimidinyl -substituted acetyltriazoles [84CH1116] In additions to various carbon-carbon triple bond systems, 2 azidothiazoles readily form the corresponding triazoles, which on photolysis yielded imidazo[4,1-*b*]thiazoles [90ZN1695] HIV activity tests have been reported for 2',3'-dideoxy-3'-(triazol-1-yl)uridenes obtained from 3-azido tetrahydrofuran derivatives by a cycloaddition reaction [90CPB2597] 2-Azido methyl-3-arylquinazolines [81M1195], 2-azidomethyloxiranes [89JOU1371] and 2-(4-pyridyl)ethylazide [88CS149] smoothly yielded the corresponding 1,2,3-triazoles In reactions with alkynes Syntheses of tris-triazoles by cycloadditions of alkynes to 4,5-di(azidomethyl)-1,2,3-triazoles have been reported [92JIC157] In spite of these and numerous other investigations in azide chemistry, no literature data

was found on cycloaddition reactions of any azidomethyl group attached to a heteroatom of a heteroaromatic ring. The synthetic application of triazolines or aziridines derived from such systems should be increased due to the activation of the methylene protons towards nucleophilic displacement. 1-(Azidomethyl)benzotriazole (**4.1a**), which is an example of such a type of azide, was recently synthesized by reaction of 1-(chloro methyl)benzotriazole with sodium azide [87JCS(P1)781]. 1-(Azidomethyl)-5-phenyl-1,2,3,4-tetrazole (**4.1b**) can similarly be obtained.



4.2, 4.3 a R = Ph, b R = CH_2Bt-1, Bt 1 = 1*H*-Benzotriazol-1-yl

Figure 4.1

4.2 Results and Discussion

1-(Azidomethyl)benzotriazole (**4.1a**) reacted with phenylacetylene, and with propargylbenzotriazole, to give mixtures of the 1,2,3-triazoles **4.2a** and **4.3a**, and **4.2b** and **4.3b**, respectively (Figure 4.1). Isomers **4.2a** and **4.3a** were isolated by column chromatography in 60% and 40% yields, and **4.2b** and **4.3b** were separated by fractional crystallization in 27% and 45% yields, respectively. The structures of

triazoles **4.2a,b** and **4.3a,b** were confirmed by NOE NMR experiments. The formation of two isomers in each case is in agreement with the previously described additions of alkyl- and aryl-azides to acetylenes [84MI559]. In contrast to the benzotriazole derivatives of type Bt-C-X (X = OR, NR_2), which are activated towards electrophilic substitution in the Grignard reaction [91JCS(P1)3295], triazoles **4.2** and **4.3** were unchanged after refluxing with PhMgX or $PhCH_2ZnX$ in toluene for several days. The reaction with phenylacetylene gave a higher yield of the 1,5-isomer, while propargylbenzotriazole gave a higher yield of the 1,4-isomer. This could be due the relatively bulky nature of the benzotriazolyl group compared to a phenyl group, causing steric hindrance between the two Bt groups in the 1,5-isomer.

The products from cycloadditions of alkenes to the azido group in **4.1a,b** depended upon the alkene structure (figure 4.3 and 4.4). Thus azides **4.1a,b** reacted with 2-vinylpyridine in refluxing toluene for 48 hours to give the respective aziridines **4.5a** (60%) and **4.5b** (40%) together with the Michael addition products **4.6a** (40%) and **4.6b** (30%). There was no detection of 1,2,3-triazoline, although this may have been the intermediate, which loses nitrogen to give aziridine **4.5**. The formation of 1-(benzotriazol-2-yl)-2-R-substituted ethanes of type **4.6** also observed in reactions of electron-deficient alkenes with 1-(*N*-morpholino)- or 1-(*N*-morpholino)-1-phenyl-methylbenzotriazole suggested that **4.1** may exists in equilibrium with its ionic form (**4.4**) and products **4.6** can be considered as a formal addition of a benzotriazolyl anion to the double bond of an alkene (figure 4.2). Reaction *via* path *b* leads to the cycloaddition product, while path *a* gives the addition product. For strained olefins, such as norbornene, the reaction follows path *b* exclusively. The structures of

azirıdines **4.5a,b** were confirmed by the chemical shifts and coupling constants of the protons in the three membered ring

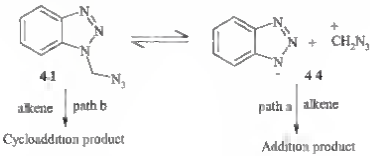
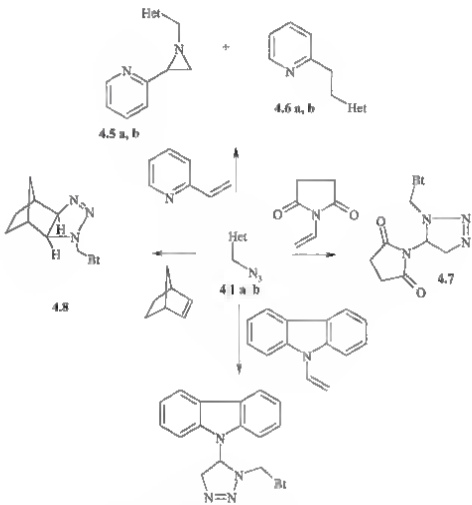


Figure 4.2

1,2,3-Triazolines **4.7**, **4.8**, and **4.9** were isolated from reactions of **4.1a** with the corresponding electron-rich alkenes in 65-85% yields. The reaction of **4.1a** with norbornene led to the *exo* isomer **4.8** as the only product isolated in 85% yield. The formation of an *exo* azirıdine isomer from the reaction of norbornene with 2-(4-pyridyl)ethyl azide [88CS149] was earlier described, where the intermediate triazoline ring formed is evidently less thermally stable than that of **4.8**. Structure **4.8** was confirmed by the strongly shielded *anti* H-bridge signal in the ^{1}H NMR spectrum (δ 0.91), which is typical for the *exo* isomers of norbornene adducts [84MI559]. Dicyclopentadiene reacted with azide **4.1a** only at the norbornene double bond to give **4.13**, in agreement with previously reported analogous additions. Triazolines **4.7**, **4.8**, **4.9** and **4.13** were stable on thermolysis up to 200 °C, and the formation of azirıdines or the ring opened products was not observed. A similar surprising thermal stability was reported for the trimethylsilyl-substituted triazoline adducts of norbornene or dicyclopentadiene with trimethylsilyl azide [76JOM285].



a, Het = 1H-Benzotriazol-1-yl b Het = 5-Phenyl-1,2,3,4-tetrazol-1-yl

Figure 4.3

The triazoline **4.13** was isolated as an inseparable mixture of the *exo* and *endo* isomers in a 2.5:1 ratio. The *endo* isomer may be stabilized in this case by an

electronic interaction of the benzotriazolyl substituent with the alkene fragment in **4.13**

Azide **4.1e** reacted with *N*-maleimide in refluxing toluene for 3 hours to give exclusively triazoline **4.10**. However, when the reaction was carried out for 24 hours, a mixture of triazoline **4.10** and the expected products of its ring transformation, aziridine **4.12** and enamine **4.11**, were isolated in a 4.2:1 ratio.

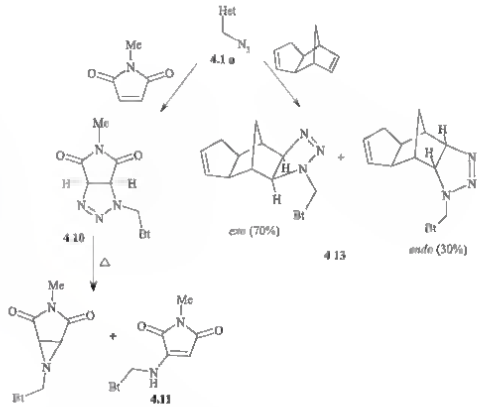


Figure 4.4

Refluxing triazoline **4.10** in toluene for 24 hours yielded a mixture of **4.12** and **4.11** in a 4:1 ratio. Thus the thermal stability of the 1,2,3-triazolines obtained was

determined by the substituents at the heterocyclic ring the higher the electron withdrawing effect of the substituent, the more readily elimination of nitrogen occurs with subsequent formation of aziridines and /or enamines. It was expected that ready lithiation at the 1 methylene group in triazolines of type **4.8** or **4.10**, and in aziridines of type **4.5** would occur, and that the anions formed should undergo electrophilic substitution similar to the examples described for 1-methoxymethylbenzotriazole [91JCS(P1)3295] However, treatment of adducts **4.8**, **4.10** and **4.5a** with *n*-butyllithium or lithium diisopropylamide at 78° in tetrahydrofuran solution, followed by addition of alkyl iodides or benzyl bromide, led to complete destruction of the starting material, and only benzotriazole was isolated in 90% yield Decomposition was also observed in reactions of the same adducts with phenylmagnesium or methylmagnesium iodide in refluxing toluene Thus, the triazoline ring in **4.7** decomposes under conditions of both electrophilic and nucleophilic substitution Similar decomposition of aziridines under basic conditions, such as Grignard reagents has been observed

In conclusion, cycloaddition reactions of 1-(azidomethyl)benzotriazole with alkynes gave mixtures of the expected isomeric (benzotriazol-1-yl)methyl-substituted 1,2,3-triazoles, but attempts to replace the benzotriazole group with Grignard reagents failed The use of alkenes as dienophiles in reactions of 1-(azidomethyl)-benzotriazole or -5-phenyl-1,2,3,4-tetrazole gave triazolines or aziridines depending upon the structure of the azide and the dienophile used.

4.3 Experimental

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. The ^{1}H and ^{13}C NMR spectra were recorded on a Gemini 300 spectrometer (300 and 75 MHz respectively) using deuteriochloroform as solvent. Elemental analyses were performed on a Carlo Erba 1106 elemental analyzer. Commercially available reagent grade solvents were dried over sodium benzophenone. Flash column chromatography was run over EM Science silica gel (230-400 mesh). 1-(Azidomethyl)benzotriazole (**4.1a**) was prepared according to the previously described method [87JCS(P1)781].

1-Azidomethyl-5-phenyl-1,2,3,4-tetrazole (4.1b). A mixture of 1-chloromethyl-5-phenyl-1,2,3,4-tetrazole (1.0 g, 5 mmoles) and sodium azide (0.5 g, 7.6 mmoles) in dimethylsulfoxide (10 ml) was stirred at room temperature for 12 hours. The mixture was poured into water (40 ml), and a colorless precipitate was filtered off, dried and recrystallized from isopropyl alcohol-hexane (1:1) to give **4.1b** (68%), mp 84-86 C, ^{1}H NMR. δ 8.17-8.22 (m, 2 H), 7.48-7.53 (m, 3 H), 5.68 (s, 2 H), ^{13}C NMR δ 166.1, 130.8, 129.0, 127.0, 126.7, 65.3. *Anal.* Calcd. for $C_8H_7N_7$: C, 47.76; H, 3.51; N, 48.73. Found: C, 47.87; H, 3.46; N, 49.01.

Reaction of 1-(Azidomethyl)benzotriazole (4.1a) with Phenylacetylene. A mixture of **4.1a** (0.52 g, 3 mmoles) and phenylacetylene (0.8 g, 3.2 mmoles) in toluene (3 ml) was refluxed for 2 hours. The solution was cooled, and hexane (10 ml) was added to form a colorless oil. The mixture was refluxed until the oil crystallized (about 3

minutes) The product was filtered off, dried and purified by flash chromatography (chloroform) to give **4.2a** (60%) and **4.3a** (40%)

1-(Benzotriazol-1-ylmethyl)-5-phenyl-1,2,3-triazole (4.2a) This compound was obtained as colorless plates (isopropyl alcohol), mp 165-168 °C, ^{1}H NMR δ 8 06 (d, 1 H, J = 8 4 Hz), 7 98 (d, 1 H, J = 8 4 Hz), 7 71 (s, 1 H) 7 53-7 60 (m, 6 H), 7 42 (dd, 1 H, J_1 = 7 5 Hz, J_2 = 7 7 Hz) 7 06 (s, 2 H), ^{13}C NMR δ 146 2, 139 0, 133 4, 132 7, 130.2, 129.3, 128 7, 125.3, 124 8, 120.0, 110 7, 57 7 *Anal* Calcd. for $C_{15}H_{12}N_6$ C, 65 21, H, 4 38, N, 30 42 Found C, 64 86, H, 4 34, N, 30 74

1-(Benzotriazol-1-ylmethyl)-4-phenyl-1,2,3-triazole (4.3a) This compound was obtained as colorless plates (isopropyl alcohol), mp 171-173 °C, ^{1}H NMR δ 8 08 (d, 1 H, J = 8.3 Hz), 8 03 (s, 1 H), 7 87 (d, 1 H, J = 8 4 Hz), 7 75-7 79 (m, 2 H), 7 53 -7 60 (m, 1 H), 7.32-7 46 (m, 4 H), 7.17 (s, 2 H), ^{13}C NMR δ 146 4, 146.2, 132 3, 129 6, 128 9, 128 8, 128 6, 125.8, 125 0, 120 2, 119 3, 109 7, 59 4 *Anal* Calcd for $C_{15}H_{12}N_6$ C 65.21, H 4 38, N, 30 42 Found C, 64 99, H, 4 35, N, 30 82

Reaction of 1-(Azidomethyl)benzotriazole (4.1a) with 1-Propargylbenzotriazole

A mixture of **4 1a** (0 16 g, 1 mmole) and 1-propargylbenzotriazole (0.20 g, 1 1 mmoles) in toluene (3 ml) was refluxed for 2 hours The solution was cooled, and **4 3b** (45%) was filtered off The filtrate was evaporated *in vacuo* to give **4.2b** (27%)

1,5-Di(benzotriazol-1-ylmethyl)-1,2,3-triazole (4 2b) This compound was obtained as colorless plates (isopropyl alcohol), mp 138 140 °C, ^{1}H NMR δ 8 04-8 09 (m, 2 H) 7 92 (d, 1 H J = 8 4 Hz), 7 66 (s 1 H) 7 41-7 62 (m, 5 H) 7 37 (s, 2 H), 6 21 (s, 2 H), ^{13}C NMR δ 146 1, 145 9, 135 2, 132 5, 132 3, 131 6, 129 1, 128.4, 125.1,

124 5, 120 4, 120.2, 109 9, 108 8, 57 6, 39 6 *Anal* Calcd. for $C_{16}H_{15}N_9$ C, 57 98, H, 3 96, N, 38 06 Found C, 57 86, H, 3 94, N, 38 39

1,4-Di(benzotriazol-1-ylmethyl)-1,2,3-triazole (4.3b) This compound was obtained as colorless plates (isopropyl alcohol), mp 208-211 °C, ^{1}H NMR δ, 8 02-8 08 (m, 2 H), 7 85 (s, 1H), 7.79 (d, 1 H, *J* = 8 4 Hz), 7 67 (d, 1 H, *J* = 8.3 Hz), 7 54-7 39 (m, 1 H), 7 32 7 48 (m 3 H), 7 06 (s, 2 H) 5 91 (s, 2 H), ^{13}C NMR δ 143 6, 129 0, 127 8, 125 1, 124.2, 123 0, 120 4, 120 1, 113 4 109 7, 109 5, 59 2, 43 3.*Anal* Calcd. for $C_{16}H_{15}N_9$ C, 57 98, H, 3 96, N, 38 06 Found. C, 57 81, H, 3 94, N, 38 40

Reaction of Azides 4 1a,b with 2-Vinylpyridine 2-Vinylpyridine (0 78 g, 7.5 mmoles) was added to the appropriate azide (5 7 mmoles) in toluene (50 ml) and the mixture was refluxed for 48 hours The reaction was monitored by tlc until the starting materials had been consumed The solvent was evaporated *in vacuo* to give an oily crude mixture of **4 5a** and **4 6a** and **4 5b** and **4 6b** which was separated by flash chromatography (benzene-acetone, 7 3) in 60% and 40%, and 30% add 20% yields, respectively

1-(Benzotriazol-1-ylmethyl)-2-(pyrid-2-yl)aziridine (4.5a) This compound was obtained as light yellow needles (ethyl alcohol) mp 98-100°C, ^{1}H NMR δ 8.40 (d, 1 H, *J* = 4.2 Hz, α-pyridyl), 8.04 (d, 1 H, *J* = 8.4 Hz, 8 H, Bt 1), 7 54 (d, 1 H, *J* = 8.3 Hz, 5-H, Bt 1), 7 47 7 58 (m, 2 H), 7 32-7 38 (m 1 H) 7 08-7 16 (m 2 H), 5 44 (d, 1 H, *J* = 12 4 Hz, CH_2Bt 1), 5 30 (d 1 H, *J* = 12 4 Hz, CH_2Bt-1), 3 07 (dd, 1 H, J_1 = 3 4 Hz, J_2 = 6 7 Hz) 2.19 (d, 1 H, *J* = 3.2 Hz, *trans*-H to methine), 2.18 (d, 1 H, *J* = 6 6 Hz, *cis*-H to methine), ^{13}C NMR δ 157 3, 149 8 149 0, 145 9, 136 4, 127 6,

124 0, 122 2, 120.5, 119 7, 109 9, 69 4, 40 4, 35.3 *Anal* Calcd. for $C_{14}H_{13}N_3$ C, 66 92, H, 5.21, N, 27 87 Found. C, 66 81 H, 5 16, N, 27 78

1-(Benzotriazol-2-yl)-2-(pyrid-2-yl)ethane (4 6a) This compound was obtained as a light yellow oil, ^{1}H NMR. δ 8 57 (m, 1 H, α-pyridyl), 7 85-7 82 (m, 2 H, 5- and 8-H, Bt-2), 7 51-7 45 (dt, 1 H, J_1 = 1 8 Hz, J_2 = 7 7 Hz γ pyridyl) 7.37-7 31 (m, 2 H, 6- and 7-H, Bt-2), 7 09-7 08 (m, 1 H, β pyridyl), 7 03 (d, 1 H, J = 7 8 Hz, β' pyridyl), 5 20 (t, 2 H, J = 7 3 Hz) 3 63 (t, 2 H, J = 7 3 Hz) ^{13}C NMR δ 157 0, 149 2, 144 0, 136.2, 125 9, 123 0, 121 6, 117 7, 55 4, 37 7 *Anal* Calcd. for $C_{13}H_{12}N_4$ C, 69 62, H, 5 39, N, 24 98 Found C, 69 29, H, 5 34, N, 25 32.

1-(5-Phenyl-1,2,3,4-tetrazol-1-yl)-2-(pyrid-2-yl)aziridine (4.5h) This compound was obtained as a light yellow oil, ^{1}H NMR δ 8 52 (d, 1 H, J = 4 7 Hz, α-pyridyl), 8 18-8 15 (m, 2 H), 7 59 (dt, 1 H, J_1 = 1 8 Hz, J_2 = 7 6 Hz, γ-pyridyl), 7 50-7 43 (m, 4 H), 7.23 (d, 1 H, J = 7 7 Hz, β-pyridyl), 5.51 (d, 1 H, J = 11 9 Hz, CH_2Bt 1), 5 36 (d, 1 H, J = 12 0 Hz, CH_2Bt-1), 3 08 (dd, 1 H, J_1 = 3 5 Hz, J_2 = 6 5 Hz), 2.28 (d, 1 H, J = 3 5 Hz, *trans*-H to methine), 2 19 (d, 1 H, J = 6 7 Hz, *cis*-H to methine) ^{13}C NMR δ 149 1, 136 4, 130 3, 128 7, 128 6 126 8, 122 3, 120.7, 72.4, 39 8, 34 6 *Anal* Calcd for $C_{15}H_{14}N_6$ C, 64 73, H, 5 07, N, 30.20 Found C, 65 00, H, 5 13, N, 30 08

1-(5-Phenyl-1,2,3,4-tetrazol-1-yl)-2-(pyrid-2-yl)ethane (4.6b) This compound was obtained as a light yellow oil, ^{1}H NMR δ 8 56 (dd, 1 H, J_1 = 0 8 Hz, J_2 = 4 9 Hz, α-pyridyl), 8 14-8 10 (m, 2 H) 7.55 (dt, 1 H, J_1 = 1 8 Hz, J_2 = 7.6 Hz, γ-pyridyl), 7 49-7 43 (m, 3 H), 7 15 7 11 (m, 1 H, β-pyridyl), 7 08 (d, 1 H, J = 7 7 Hz,

β[1] pyridyl), 5 10 (t, 2 H, J = 7 3 Hz) 3.54 (t, 2 H, J = 7 3 Hz), ^{13}C NMR δ 164 8, 156 4, 149 5, 136 4, 130 1, 128 8, 128 7, 126 6, 123.2, 121 9, 52 1, 37 1 *Anal.* Calcd. for $C_{14}H_{13}N_5$ C 66 92, H, 5.21, N, 27 87 Found C 66 69, H, 5 15, N, 27 96

Reaction of Azides 4.1a,b with 1-Vinylpyrrolid-2-one and with 1-Vinylcarbazole

A mixture of azide **4 1a** or **4 1b** (1 5 mmoles) and the appropriate dienophile (2 mmoles) in toluene (50 ml) was refluxed for 24 hours. The solvent was removed *in vacuo* to give crude compounds **4.7a**, **4.7b**, and **4.9** in 75%, 83% and 80% yields, respectively

1-(Benzotriazol-1-ylmethyl)-4-(pyrrolid-2-on-1-yl)-Δ^2-1,2,3-triazoline (4.7a) This compound was obtained as colorless plates (ethyl alcohol), mp 155-156 °C; ^{1}H NMR δ 8 04 (d, 1 H, J = 8 4 Hz), 7 90 (d 1 H, J = 8 4 Hz), 7.58-7 53 (m, 1 H), 7 44-7.38 (m, 1 H), 6 53 (s, 2 H), 6 06 (dd 1 H, J_1 = 3 3 Hz, J_2 = 9 9 Hz) 4 25 (dd, 1 H, J_1 = 3 3 Hz, J_2 = 17 6 Hz), 4 11 (dd, 1 H, J_1 = 9 9 Hz, J_2 = 17 6 Hz), 2.81-2 74 (m, 1 H), 2 39-2 18 (m, 2 H), 1 80-1 64 (m, 2 H), 1 48-1 32 (m, 1 H) ^{13}C NMR δ 175 6, 145 8, 132.5, 128 0, 124 3, 119 6, 110 2, 67.6, 60 7, 57 6, 41.4, 30 1, 16 7 *Anal.* Calcd for $C_{13}H_{15}N_7O$ C, 54 73, H, 5.30, N, 34.37 Found C, 54.38, H, 5 26, N, 34 64

1-(Benzotriazol-1-ylmethyl)-4-(carbazol-1-yl)-Δ^2-1,2,3-triazoline (4.9) This compound was obtained as light yellow needles (benzene-hexane, 1.1), mp 156-158 °C, ^{1}H NMR δ 8.07 8 04 (m, 2 H), 8 00-7 96 (m, 1 H), 7 63-7 60 (m, 1 H), 7 49-7 24 (m, 8 H) 6 45 (d, 1H, J = 15.2 Hz, C$\underline{H}_2$Bt), 6 40 (dd, 1 H, J_1 = 5 6 Hz, J_2 = 12 0 Hz), 5 85 (d, 1 H J = 15.2 Hz, C$\underline{H}_2$Bt), 4.67 (dd, 1 H, J_1 = 5 6 Hz, J_2 = 18.5 Hz), 4 45 (dd,

1 H, J_1 = 12 0 Hz, J_2 = 18.5 Hz), ^{13}C NMR δ 146 1, 132 3, 128 1, 126 4, 124 4, 120 7, 120 6, 119 9, 109 7, 69 0, 62.4, 56 9 *Anal.* Calcd for $C_{21}H_{17}N_7$ C, 68 65, H, 4 66, N, 26 69 Found C, 68 96, H, 4 74, N, 26 58

1-(5-Phenyl-1,2,3,4-tetrazol-1-ylmethyl)-4-(pyrrolid-2-on-1-yl)-Δ^2-1,2,3-triazoline (4 7b) This compound was obtained as light yellow prisms (benzene-hexane, 1 1), mp 98-101 °C, ^{1}H NMR. δ 8 18-8 15 (m, 2 H), 7 51-7 48 (m, 3 H), 6 53 (d, 1 H, *J*=14 6 Hz, CH$_2$Bt) 6 46 (d, 1 H, *J* = 14 6 Hz CH$_2$Bt), 6 11 (dd, 1 H, J_1 = 3 3 Hz, J_2 = 9 9 Hz), 4 32 (dd, 1 H, J_1 = 3 5 Hz, J_2 = 17 8 Hz), 4.20 (dd, 1 H, J_1 = 9 9 Hz, J_2=17 8 Hz) 3 00-2 92 (m 1 H), 2.78-2.23 (m, 3 H), 1 90-1 75 (m, 1 H), 1 73-1 55 (m, 1 H), ^{13}C NMR δ 175 6, 165 4, 130 5 128 8 126 7 126 6 67 9, 62 1, 60 5, 41 5-30.2 16 9 *Anal* Calcd for $C_{14}H_{16}N_8O$ C, 53 84, H, 5 16, N, 35 88 Found. C, 54 17, H, 5 17, N, 35 76

Synthesis of Adducts 4.7, 4.9, 4.10, 4.11 and 4.13 A mixture of azide **4.1a** or **4.1b** (5 7 mmoles) and the appropriate dienophile (7 5 mmoles) in toluene (30 ml) was refluxed for 24 hours for adducts **4.8**, **4.13** and **4 12** and 4 11, and 3 hours for adduct **4.10** The solvent was removed *in vacuo* to give a residue which crystallized on addition of a few drops of diethyl ether, and then was recrystallized from ethyl alcohol to give **4.8** (85% yield) **4 13** (65% yield), **4 10** (80% yield), and a mixture of **4.12** and **4.11** (4 1) (80% yield)

1-(Benzotriazol-1-ylmethyl)-4,7-methano(3a,4,5,6,7,7a)hexahydrobenzotriazole (4 8) This compound was obtained as colorless plates mp 128 130 °C, ^{1}H NMR δ 8 05 (d, 1 H, *J* = 8 5 Hz), 7 75 (d, 1 H, *J* = 8 2 Hz), 7 51 (dd, 1 H, J_1 = 7 4 Hz, J_2= 7 8

Hz), 7 40 (dd, 1 H, J_1 = 7 4 Hz, J_2 = 7 9 Hz), 6 53 (d, 1 H, J = 14 8 Hz, C$\underline{H}_2$Bt), 6.35 (d, 1 H, J = 14 8 Hz, C$\underline{H}_2$Bt), 4 31 (d, 1 H, J = 9 3 Hz, 4-H), 3 23 (d, 1 H, J = 9 3 Hz, 5-H), 2 65-2 62 (m, 1 H), 2.23-2.20 (m, 1 H), 1 50-1 44 (m, 2 H), 1 23-1 13 (m, 2 H), 1 04 (dd, 1 H, J_1 = 1 3 Hz, J_2 = 10 5 Hz, *anti* of bridge), 0 91 (dd, 1 H, J_1 = 1 5 Hz, J_2 = 10 7 Hz, *syn* of bridge), ^{13}C NMR. δ 146.3, 132.3, 128 0, 124 4 119 8, 110.3, 88.2, 59 83, 59 78, 41 1, 40 5, 32.2, 25 6, 24 4 *Anal* Calcd. for $C_{14}H_{16}N_6$ C, 62 69, H 5 97 N, 31.34 Found C, 62 90; H, 6 03, N 31 26

Inseperable Mixture of exo and endo Isomers (2.5 1) of Adduct (4.13) This mixture was obtained as colorless plates, mp 133-135 °C, ^{1}H NMR (the signals of the minor isomer are in square brackets) δ 8 06 (d, 1 H, J = 8.3 Hz) [8 06 (d, 1 H, J = 8.3 Hz)], 7 77-7 74 (m, 1 H) [7 77-7 74 (m, 1 H)], 7 53-7 39 (m, 1 H) [7 53-7 39 (m, 1 H)], 6 48 (d, 1 H, J = 14.8 Hz, C$\underline{H}_2$Bt) [6.50 (d, 1 H, J = 14 9 Hz, C$\underline{H}_2$Bt)], 6 37 (d, 1 H, J = 14 9 Hz, C$\underline{H}_2$Bt) [6 35 (d, 1 H, J = 14 9 Hz, C$\underline{H}_2$Bt)], 5 60-5 50 (m, 2 H) [5 60-5 50 (m, 2 H)] 4 32 (d, 1 H, J = 9 6 Hz) [4 28 (d, 1 H, J = 9 6 Hz)], 3 18 (d, 1 H, J = 9 6 Hz) [3.25 (d, 1 H, J = 9 6 Hz)], 3 13-3 08 (m, 1 H) [3 13-3 08 (m, 1 H)]- [2.76 (d, 1H, J = 5 3 Hz)], 2.60-2.50 (m, 2 H) [2 60-2.50 (m, 2 H)], 2 34 (d, 1 H, J=4.7 Hz), 2.30-2.20 (m, 3 H) [2.30-2.20 (m, 2 H)], [2 11 (d, 1 H, J = 4 4 Hz)], 1 26 -1 18 (m, 1 H) [1 26-1 18 (m, 1 H)], 1 00-0 94 (m 1 H) [1 00-0 94 (m, 1 H)], ^{13}C NMR (some signals are coalesced) δ 146 2, 132.3, 131 6, 131 2, 130 82, 130 78, 127 9, 124 3 119 7 110 23, 110 21 85 4, 82 2, 59 8 59 7, 57 2, 54 5, 51 4, 51 1, 46 0, 45 2, 44 2, 43 5, 40 7 40 3, 34 9 34 7 32 0 31 7 30 8 *Anal.* Calcd for $C_{17}H_{18}N_6$ C, 66 65, H, 5 92 N, 27 43 Found C 66 52, H, 5 96, N, 27 07

2-(Benzotriazol-1-ylmethyl)-6,8-dion-7-methyl-2,3,4,7-tetraazabicyclo-[3.3.0^{1,5}]-octane (4.10) This compound was obtained as light yellow prisms, mp 133-135 °C, ^{1}H NMR (dimethylsulfoxide-d_6) δ 8.11 (d, 1 H, J = 8.4 Hz), 7.92 (d, 1 H, J = 8.4 Hz), 7.64-7.61 (m, 1 H), 7.49-7.46 (m, 1 H) 7.00 (d, 1 H, J = 15.4 Hz, CH_2Bt) 6.53 (d, 1 H, J = 15.4 Hz, CH_2Bt), 5.70 (d, 1 H, J = 10.5 Hz) 4.40 (d, 1 H, J = 10.5 Hz), 2.80 (s, 3 H), ^{13}C NMR (dimethylsulfoxide-d_6) δ 172.4, 170.5, 145.3, 132.5, 127.9, 124.4, 119.3, 110.5, 84.2, 59.2 56.7, 24.7 *Anal.* Calcd. for $C_{12}H_{11}N_5O_2$ C, 50.53, H, 3.89, N, 34.37 Found C, 50.52, H, 3.89, N, 34.66

2-(Benzotriazol-1-ylmethyl)-4,6-dion-5-methyl-2-azabicyclo[2.2.1]^{1,3}[hexane (4.10) and 3-(Benzotriazol-1-ylmethylamino)-1-methylmaleimide (4.11) This mixture was obtained as colorless plates mp 168-170 °C, ^{1}H NMR (dimethylsulfoxide-d_6) (the signals of 4.11 are in square brackets) δ [8.98-8.90 (broad m, 1 H, NH)], 8.15-8.11 (m, 1 H), [8.15-8.11 (m, 1 H)], 8.07-8.04 (m, 1 H), [8.07-8.04 (m, 1 H)], 7.86-7.62 (m, 1 H), [7.86-7.62 (m, 1 H)], 7.52-7.44 (m, 1 H), [7.52-7.44 (m, 1 H)], [6.14 (d, 2 H, J = 5.8 Hz, CH_2Bt)], 5.50 (s, 2 H, CH_2Bt), [5.31 (s, 1 H)], 3.88 (s, 2 H) [2.79 (s, 3 H)], 2.68 (s, 3 H), ^{13}C NMR (dimethylsulfoxide-d_6) (the signals of 4.11 are in brackets) δ 171.6, (166.8, 148.5) 145.4, (145.4), 132.5, (131.6), 128.1, (127.9), 124.4, (124.4), 119.3, (119.3, 110.8), 110.7, 65.8, (55.6), 23.9, (23.6) *Anal* Calcd for $C_{12}H_{11}N_5O_2$ C, 56.03, H, 4.31, N, 27.22 Found C, 56.14, H, 4.31, N, 27.52

CHAPTER V
ADDITION REACTIONS OF IMMONIUM BENZOTRIAZOLATES TO ACETYLINIC ESTERS

5.1 Introduction

Triple bonds polarized by functional groups such as esters are very reactive, and are attacked readily by many nucleophiles. Several reactions of acetylenic esters employing various nucleophiles are reported in the literature [67AG423]. Nucleophiles in general add to acetylenic esters giving rise to simple 1:1 adducts, arising out of a Michael type of addition [67AG423]. Several studies on the addition of amines to acetylenic esters have been reported [73ACSA2802, 76TL4061, 80JHC881, 80LA997, 93SC817], giving both the *trans* and *cis* isomers, depending on the reaction conditions and the steric nature of the amine [67AG423]. Addition of alcohols similarly gives both the *trans* and *cis* enol ethers [67AG423]. If the attacking nucleophiles contain suitably positioned functional groups (carbonyl or double bonds), the intermediates formed in these reactions could undergo cyclization to give heterocyclic compounds.

It has been shown that compounds such as **5.1**, readily formed by the condensation of an aldehyde, a secondary amine and benzotriazole [88JCS(P1)2339, 93JHC381], undergo reversible dissociation. An equilibrium with a finite quantity of ion pairs **5.3** [75JCS(P1)118], 93JOC812] is established, which mediates the

tautomerism in solution with the isomeric species **5.4** [93JOC4049] Such compounds (**5.1**) are valuable synthetic intermediates and react with a wide variety of simple nucleophiles to give products **5.5** in which the benzotriazolyl group has been replaced [91T2683] Recently Katritzky and his group described addition reactions of **5.1** with electron rich olefins (vinylamines [92JPR114] and vinyl ethers [93JOC4049]) to give addition products **5.2** (figure 5 1)

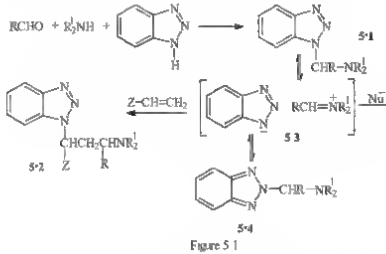


Figure 5 1

In the formation of **5.2**, the first step is undoubtedly addition of the immonium cation from **5.3** to the electron rich olefin to give **5.6**

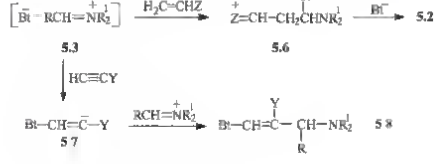


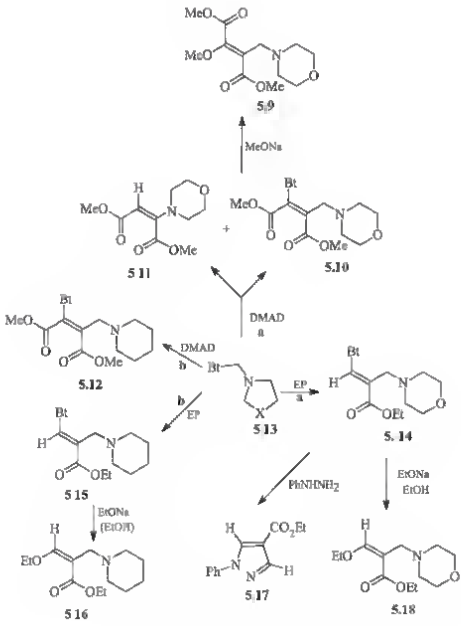
Figure 5.2

The addition of nucleophiles followed by H to electron-deficient double bonds is the familiar Michael reaction[69T527, 67AG423] However, examples in which the product from nucleophilic addition to an electron-deficient C=C subsequently adds a carbon electrophile are rare although the familiar nucleophilic induced polymerization of electron-deficient olefins [59JCS3858, 60JCS928] falls into this category Results presented in this chapter demonstrate that a stepwise reaction in the opposite sense is possible for certain electron deficient acetylenes with the formation of **5.8** via intermediate **5.7** (figure 5.2).

5 2 Results and Discussion

Reactions of Dimethyl Acetylenedicarboxylate (DMAD)

The reaction of 1-(morpholinomethyl)benzotriazole (**5.13a**) with dimethyl acetylenedicarboxylate gave the adduct **5 10** (30%) together with dimethyl morpholinomaleate (**5.11**) resulting from a simple addition product of morpholine to dimethyl acetylenedicarboxylate (figure 5.3) (The preparation of compound **5.11** has been previously reported [60DOK847]) Compounds **5.11** and **5.10** were separated by column chromatography (figure 5 3). It was elucidated from the NMR spectra and NOE experiments that structure **5 10** contains *cis*-carboxylate groups. When the singlet at 5.57 ppm (2 H) was irradiated, a positive NOE occured at 3.35 ppm (t, 4 H) and at 7 68 ppm (d, 1H), indicating a *cis* relationship between the 1-morpholinomethyl and the benzotriazole groups. Similarly **5 11** was shown to be the maleate isomer by a positive NOE on the alkenyl proton (4 53 ppm) when the protons of the morpholino group at 2 87 ppm were irradiated.



EP = ethyl propiolate, DMAD = dimethyl acetylenedicarboxylate.

a X = $-CH_2O-$, b X = $-(CH_2)_2-$

Figure 5.3

When the two methyl groups (3.38 and 3 75 ppm) were irradiated a positive NOE at 4 53 ppm was observed only on irradiation of the 3 38 ppm methyl group, indicating that the alkenyl proton was adjacent to the methyl group at 3 38 ppm. The reaction of 1-(piperidinomethyl)benzotriazole (**5 13b**) with dimethyl acetylenedicarboxylate gave the addition product **5 12** The structure was assigned by ^{1}H and ^{13}C NMR.

Reactions of Ethyl Propiolate

1-(Morpholinomethyl)benzotriazole (**5 13a**) and ethyl propiolate in the presence of 1 2 equivalents of ZnBr gave the addition product **5 14** in 80% isolated yield after 6 days. The structure of **5.14** (figure5 3) was assigned from the CHN analysis and NMR spectra. A positive NOE observed at 7 75 ppm (1 H) when the signal at 5 65 ppm (2 H) was irradiated indicates a *cis* relationship between the 1-morpholinomethylene group and the benzotriazole moiety

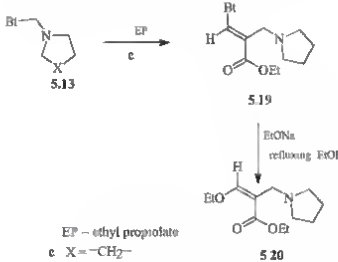
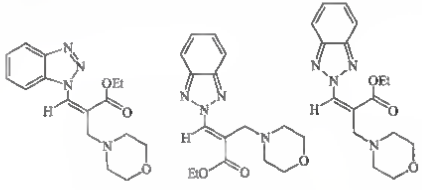


Figure 5 4

However, the conversion of **5 13a** to **5 14** was more complex than a simple addition to a single product. The ^{1}H and ^{13}C NMR spectra showed the presence of

four isomeric products in the reaction mixture after 3 days At this time, the ^{1}H NMR spectrum showed four singlets at δ 5 41 (2 H), 5.56 (2 H), 5 67 (2 H) and 5 80 (2 H), having intensities in the ratio 2 3 1 2, each corresponding to a methylene group adjacent to a double bond. The aromatic region showed the presence of both Bt^1 (benzotriazol-1-yl) (7 85-8 1 m, 7 6, t, 7 0-7 5, m) and Bt^2 (benzotriazol-2-yl) groups (7 70-7 8, m, 7 2-7 4, m) The ethoxy and morpholino signals appeared as multiplets as a result of overlap of peaks for the different isomers. Thus, at this stage of the reaction, product **5 14** was accompanied by **5.21 5 22** and **5.23** (figure 5.5)



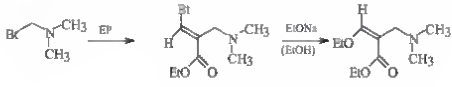
5.21 **5.22** **5.23**

Figure 5 5

Compounds **5.21 5.23** were evidently formed under kinetic control and as the reaction proceeded, the thermodynamically more stable **5.14** was ultimately formed exclusively as evidenced by the NMR structure of the reaction mixture.

Ethyl propiolate formed products **5 15** (57%) and **5.19** (54%) with 1-(piperidinomethyl)- (**5 13b**) and 1-(pyrolidinomethyl)-benzotriazole (**5.13c**) The structures, similar to that of **5.14**, were assigned similarly By analogy, the reaction

of benzotriazol-1-yl-*N,N*-dimethylmethane (**5 24**) with ethyl propiolate gave the addition product **5 25** (figure 5 6)



5.24 **5 25** **5.26**

Figure 5 6

Transformations of Initial Adducts of Immonium Benzotriazolates and Acetylenic Esters

The benzotriazole residum in the products were readily replaced by nucleophiles, as expected for an addition-elimination sequence Thus, treatment of **5.14** with ethanolic sodium ethoxide gave ethoxy derivative **5.18** Complete assignments for the proton and carbon chemical shifts of **5 18** were made on the basis of the proton-carbon direct couplings determined by HETCOR experiments A positive NOE at 3 54 ppm was observed when the alkenyl proton (7 47 ppm) was irradiated, indicating a *cis* relationship between the alkenyl proton and the morpholino moiety Treatment of **5.19** and **5.25** with ethanolic sodium ethoxide gave **5 20** and **5.26** respectively

Compound **5 10** was similarly converted by MeOH-NaOMe to analog **5.19** Phenylhydrazine displaced both the benzotriazole and morpholine groups in **5.14** to give **5.17**. The structure of **5 17** was assigned on the basis of the ^{1}H - ^{13}C direct couplings determined by HETCOR experiments Similar syntheses of **5.17** have been described in the literature [64CA14272a]

5.3 Experimental

Melting points were determined on a Thomas-Hoover capillary melting point apparatus or on a Kofler hot-plate microscope and are uncorrected. ^{1}H and ^{13}C NMR spectra were obtained on either a Varian VXR 300 MHz or a Gemini 300 MHz spectrometer with tetramethylsilane as the internal standard. Coupling constants are given in Hz. The structures of compounds **5.9-17** were assigned using NOEDIF, INAPT and bi-dimensional NMR experiments (COSY, HETCOR). Low resolution mass spectra were recorded on a Hewlett-Packard 5890 gas chromatography equipped with a Hewlett-Packard 5972 mass selective detector. Compounds **5.13a-e** were prepared according to literature method [89OPP135]

Reactions of Diethyl Acetylenedicarboxylate

a) With 1-(morpholinomethyl)benzotriazole. DMAD (0.7 g, 0.7 mmol) was added to a solution of 1-(morpholinomethyl)benzotriazole (**5.13a**) in toluene (50 ml) at 40-60 °C. $ZnBr_2$ (0.07 g, 0.3 mmol) was added and the reaction maintained at 60-80 °C for 72 hours. The reaction was monitored by GC. The reaction mixture was cooled to room temperature and washed with water (3 x 50 ml), the organic layer separated and dried (anhydrous Na_2SO_4) and the solvent removed *in vacuo*. The residue was recrystallized from ethanol to give a mixture of **5.11** and **5.10**. The two compounds were separated by flash column chromatography. The first compound eluted was **5.11** (eluent: methylene chloride), yield 30%. ^{1}H NMR: δ 2.87 (m, 4 H), 3.38 (s, 3 H), 3.48 (m, 4 H), 3.75 (s, 3 H), 4.53 (s, 1 H), ^{13}C NMR: δ 47.06, 50.73, 52.75, 65.72,

87 00 154 62, 167 57 HRMS (FAB) m/z = 230 1139 (m^+ + 1, 100%, $C_{18}H_{18}O_5N$ requires 230 1028) The second compound eluted was **5.10** (eluent methylene chloride) which was further recrystallized from diethyl ether in 35% yield, mp 124 °C ^{1}H NMR: δ 3 60 (s, 3 H), 3 72 (br, 4 H), 3 82 (s, 3 H), 5 57 (s, 2 H), 7 36 (t, J = 8.3Hz, 1 H), 7 49 (t, J = 8 3Hz, 1 H), 7 69 (d, J = 8 4Hz, 1 H), 8 04 (d, J = 8 4 Hz, 1 H), ^{13}C NMR δ 44 9, 49 7 50 7, 50 9, 65 6, 100 1 109 3, 118 7, 122 8, 126 2, 132 2, 144 8, 153 9, 165 1 166 7 Anal Calcd for $C_{17}H_{20}N_4O_5$ C 56 56, H 5 56, N 15 56. Found C 56 30, H 5 57, N 15 46.

b) With 1-(piperidinomethyl)benzotriazole A mixture of 1-(piperidinomethyl) benzotriazole (**5.13b**) (1 g, 4 6 mmol) and DMAD (0 66 g, 4.6 mmol) in toluene (50 ml) at 40-60 °C was treated with $ZnBr_2$ (0 07 g) The temperature was maintained at 60-100 °C for 6 days The reaction mixture was cooled, washed with water (3 x 50 ml) the organic layer separated and dried (anhydrous Na_2SO_4) and the solvent removed *in vacuo* The residue was treated with diethyl ether (5ml) to give **5.12** in 56% yield. ^{1}H NMR: δ 1 35 (br, 6 H), 3 35 (br, 4 H), 3.59 (s, 3 H), 3 85 (s, 3 H), 5 59 (s, 2 H), 7 40 (t, J = 8 0Hz, 1 H), 7 46 (t, J = 8 0Hz, 1 H), 7 68 (d, J = 8 1Hz, 1 H) 8 02 (d, J = 8 1Hz, 1H); ^{13}C NMR δ 23 3, 25 9, 46.5, 51 5, 51.6, 52.5, 96.7 110.4, 119 4, 123 6, 126 9, 132.9, 145 7, 155 7, 166.5, 168.2 HRMS (FAB) m/z =359 1576 (m^++1, 2 17%, $C_{18}H_{23}N_4O_4$ requires 359 1719)

Reactions of Et6yl propiolate

a) Wit6 1-(morp6olinomethyl)benzotriazole A mixture of 1-(morpholinomethyl) benzotriazole (**5 13a**) (1 5 g, 7 mmol) and ethyl propiolate (0 7 g, 7 mmol) in toluene (50 ml) at 40-60 °C was treated with 1.2 equivalents of $ZnBr_2$ for 6 days The reaction

was monitored by GC The reaction mixture was cooled, filtered, washed with water (3 x 50 ml), dried (anhydrous Na_2SO_4) and the solvent removed *in vacuo* The residue was treated with diethyl ether (5 ml) and the precipitate formed was filtered, washed with diethyl ether (50 ml) and dried to give **5 14** in 80% yield, mp 105 °C ^{1}H NMR δ 1 22 (t, *J* = 7 0Hz, 3 H), 3 67 (br, 4 H), 3 72 (br, 4 H), 4.18 (q, *J* = 7 0Hz, 2 H), 5 65 (s, 2H), 7 33 (t, *J* = 8 0Hz, 1 H), 7 34 (t, *J* = 8 0Hz, 1 H), 7 74 (s, 1 H), 7 75 (d, *J* = 8 0Hz, 1 H), 8 02 (d, *J* = 8 1 Hz, 1 H) ^{13}C NMR δ 14 3, 43 8, 50 8, 59 9 66 2, 90 1, 110 7, 119 1, 123 5, 126 7, 132 7, 145 5, 150 2, 169 3 Anal Calcd. for $C_{16}H_{20}NO_4$ C 60 57, H 6 33, N 17 72 Found. C 60 76, H 6 33, N 17 85

b) With 1-(piperidinomethyl)benzotriazole A mixture of 1-(piperidinomethyl) benzotriazole **(5.13b)** (1 5 g, 6 8 mmol) and ethyl propiolate (0 67 g, 6 8 mmol) at 40 -60 °C was treated with $ZnBr_2$ for 3 days. The reaction mixture was cooled to room temperature filtered and washed with water (3 x 50 ml) The organic layer was dried (anhydrous Na_2SO_4) and the solvent removed *in vacuo* The residue was treated with diethyl ether (5 ml) to give **5 15** in 50% yield ^{1}H NMR. δ 1 18 (t, *J* = 6 8Hz, 3 H), 1 65 (br, 6 H), 3 60 (br, 4 H), 4 12 (q, *J* = 6 8Hz, 2 H), 5 64 (s, 2 H), 7 25 (s, 1 H), 7 35 (t, *J* = 8 0Hz, 1 H), 7 58 (t, *J* = 8 1Hz, 1 H), 7 69 (d *J* = 8 0Hz, 1 H), 7 95 (d, *J* = 8 0Hz, 1 H), ^{13}C NMR δ 14 2, 23 8, 26 1, 44 6, 52 6, 59 9, 88.2 111 1, 119 1, 123 5, 126 7, 132 9, 145 9, 150 6, 170 1 HRMS (FAB) m/z = 315 1828 (m^+ + 1, 23 7%, $C_{17}H_{23}O_2N_4$ requires 315 1821)

c) With 1-(pyrrolidinomethyl)benzotriazoleA mixture of 1-(pyrrolidinomethyl) benzotriazole (**5.13c**) (1 5 g, 7.43 mmol) and ethyl propiolate (0 74 g, 7 4 mmol) at 40-60 °C was treated with $ZnBr_2$ for 3 days The reaction mixture was cooled to

room temperature, filtered and washed with water (3 x 50 ml) The organic layer was dried (anhydrous Na_2SO_4) and the solvent removed *in vacuo* The residue was treated with diethyl ether (5 ml) to give **5 19** in 20% yield ^{1}H NMR δ 1 23 (t, *J* = 6.7Hz, 3 H), 1 90 (br, 4 H), 3 72 (br, 4 H), 4.12 (q, *J* = 6 7Hz, 2 H), 5.62 (s, 2 H), 7 38 (t, *J* = 8 1Hz, 1 H), 7 45 (t, *J* = 8 1Hz, 1 H), 7 82 (d, *J* 8 0Hz, 1 H), 8 02 (d, *J* 8 0Hz, 1 H), ^{13}C NMR. δ 14 1, 25.2, 43 9, 59 6, 60 2, 90 1, 111 1 119.2, 123.5, 126 6 132.5, 158 6, 148 9, 168 6 HRMS (FAB) m/z = 301 1750 (m^+ + 1, 2.33%, $C_{14}H_{21}O_2N_4$ requires 301 1660)

d) With benzotriazol-1-yl-2-*N*,*N*-dimethylimethane To a solution of benzotriazol -1-yl 2-*N*,*N*-dimethylmethane (**5.24**) (1.5 g, 8 7 mmol) in toluene (50 ml) was added ethyl propiolate (0 86 g, 8 7 mmol) and $ZnBr_2$ (0 07 g) The mixture was maintained at 60-80 °C with stirring for 4 days. The reaction mixture was cooled, filtered, washed with water (3 x 50 ml), dried (anhydrous Na_2SO_4) and the solvent removed *in vacuo* The residue was treated with diethyl ether (5 ml) to give **5 25** in 80% yield ^{1}H NMR δ 1.23 (t, *J* = 6 0Hz, 3 H) 3 25 (s, 6 H), 4 15 (q, *J* = 6 0Hz, 2 H), 5 69 (s, 2 H), 7 32 (t, *J* = 7 8Hz, 1 H), 7 45 (t, *J* = 8 0Hz, 1 H), 7 65 (s, 1 H), 7 80 (d, *J* = 8 0Hz, 1 H), 8 02 (d, *J* = 8 0Hz, 1 H), ^{13}C NMR δ 14 5, 43.5, 43 6, 59 7, 89 7, 111 0, 119.3, 123 5, 126 7, 133 0, 145 8, 151 9, 169 7 HRMS (FAB) m/z = 275 1520 (m^+ + 1, 14 1%, $C_{14}H_{19}O_2N_4$ requires 275 1508)

Replacement of benzotriazole with sodium methoxide

A solution of the benzotriazole adduct **5.10** (0 72 g, 2 mmol) in methanol (20 ml) was treated with sodium metal (0 07 g, 3 mmol), under reflux for 8-10 hours until no starting material was observed by GC The mixture was cooled, poured into water and

extracted with methylene chloride The organic extract was washed with brine (2 x 50 ml) and dried (anhydrous Na_2SO_4) The solvent was removed *in vacuo* to give **5.9** in 98% yield. ^{1}H NMR δ 3 3 (s, 3 H), 3 42 (t, 4 H), 3 68 (s, 3H), 3 70 (m, 4 H), 3 85 (s, 3 H), 4 14 (s, 2 H), ^{13}C NMR. δ 50.2, 58 8, 62.9, 63 8, 66 1, 93 4, 150 0, 169.2.

General procedure for the replacement of benzotriazole with sodium ethoxide

A solution of the benzotriazole adduct (2 mmol) in ethanol (20 ml) was treated with sodium metal (3 mmol) and the mixture heated under reflux for 8-10 hours, until no starting material was detected by GC The reaction mixture was cooled, poured into water (150 ml) and extracted with methylene chloride The organic extract was washed with brine (2 x 50 ml) and dried (anhydrous Na_2SO_4) The solvent was removed to give the products in good yields.

5.18 98% yield, ^{1}H NMR δ 1 18 (t, 3 H), 1.25 (t, 3 H), 3 48 (q, 2 H), 3.54 (t, 4 H), 3 70 (dd, 4 H), 3 79 (s, 2 H), 4 14 (q, 2 H), 7 47 (s, 1 H), ^{13}C NMR δ 14 0, 14 7, 50.2, 58 8, 63 8, 63 9, 66.1, 93 4, 150 0 169 2 Anal Calcd. for $C_{12}H_{21}NO_4$ C 59.25, H 8 64, N 5 76 Found. C 58 94, H 8 75, N 5 96

5 16 80% yield, ^{1}H NMR δ 1 18 (t, 3 H), 1 21 (t, 3 H) 1 60 (br, 4 H), 3 18 (br, 2 H), 3 50 (br, 4 H), 4 15 (q, 2 H), 4 16 (q 2 H), 4 28 (s, 2 H), 7 54 (s, 1 H), ^{13}C NMR. δ 14 1, 15 1, 23 0, 26 4, 52.0, 52.3 63 8, 63 9 150 9, 151 9, 170 4

5 28 60% yield, ^{1}H NMR δ 1 28 (t 6 H) 1 95 (br, 4 H), 3 52 (q, 2 H) 3 6 (br, 4 H), 4 15 (q, 2 H), 4 3 (s, 2 H), 7 72 (s, 1 H), ^{13}C NMR δ 14 5, 15 4, 25.3, 58 6, 59 1, 63 5, 64.5, 84 6, 148 5 170 1

5.26 85% yield. ^{1}H NMR δ 1.28 (t, 3 H), 1.29 (t, 3 H), 3.18 (s, 6 H), 3.51 (q, 2 H), 4.14 (q, 2 H), 4.30 (s, 2 H), 7.51 (s, 1 H), ^{13}C NMR δ 14.5, 15.3, 42.7, 59.2, 63.1, 64.4, 152.1, 170.2.

Reaction of benzotriazole adduct (5.14) with phenylhydrazine

Compound **5.14** (0.64 g, 10 mmol) was treated with phenylhydrazine (0.12 g, 12 mmol) and heated to 100 °C for 10 hours until no starting material was detected by GC. The reaction mixture was extracted with diethyl ether (20 ml), and then with brine (3 x 50 ml). The organic layer was dried (anhydrous Na_2SO_4) and the solvent removed *in vacuo*. The residue was chromatographed on alumina and eluted with methylene chloride to give compound **5.17** in 75% yield, mp 90-93 °C. ^{1}H NMR δ 1.40 (t, 3 H), 4.35 (q, 2 H), 7.35 (t, 2 H), 7.48 (t, 1 H), 7.72 (d, 2 H), 8.12 (s, 1 H), 8.42 (s, 1 H), ^{13}C NMR δ 14.4, 29.7, 119.6, 127.5, 129.6, 129.7, 130.0, 142.2, 145.5, 168.0.

CHAPTER VI
1-(*t*-BUTOXYCARBONYL)BENZOTRIAZOLE AND 1-(*p*-METHOXYBENZYLOXYCARBONYL)BENZOTRIAZOLE AND THEIR USE IN THE PROTECTION OF AMINO ACIDS

6.1 Introduction

The *N*-protection of amino acids is essential in many peptide syntheses [93MI1] Among a wide variety of protecting groups, *t*-butoxycarbonyl (BOC) and benzyloxycarbonyl (Cbz) groups are of fundamental importance due to their availability, effective protection and ready cleavage [91MI1327] Some of the reagents used are less attractive because of disadvantages such as difficult access or insufficient reactivity of the reagents, or cumbersome elimination of by-products from the protected amino acids Hence, although many reagents are available to introduce BOC and Cbz, novel inexpensive, easy to-prepare, stable, and effective reagents are still in demand, especially in industry 1-(*t*-Butoxycarbonyl)benzotriazole (BOC-Bt) (**6.4**) was previously reported in a patent as prepared from BtCOCl [90CA539] 1-(Benzyloxycarbonyl)-benzotriazole (Cbz-Bt) was previously prepared esther from benzyloxycarbonyl chloride and benzotriazole [75JHC665, 86S958] or from (benzotriazol-1-yl)carbonyl chloride and benzyl alcohol [77S704], and has been employed for the protection of amino functions in peptide synthesis [86S958] However, the analog 1-(*p*-methoxybenzyloxycarbonyl) benzotriazole (Moz-Bt) (**6.5**) has not been

reported previously For many applications, Moz-Bt should be more useful than Cbz-Bt since the Moz group is more readily cleaved by acid than the Cbz or BOC group [91MI1327]

This chapter reports the convenient preparation of 1-(*t*-butoxycarbonyl) benzotriazole (BOC-Bt) **(6.4)** and 1-(*p*-methoxybenzyloxycarbonyl)-benzotriazole (Moz-Bt) **(6.5)** and their application in the protection of amino acids.

6.2 Results and Discussion

(Benzotriazol 1-yl)carbonyl chloride **(6.3)** was prepared by addition of a solution of benzotriazole **(6.1)** in THF into a 20% solution of phosgene **(6.2)** in toluene at -20 °C as shown in Scheme 6 1 Excess phosgene (4 eq) is essential in order to avoid the over-substitution of **6.3** with benzotriazole. After the reaction was complete removal of solvents under reduced pressure gave compound **6.3** in high purity, which was used without further purification for the synthesis of BOC-Bt 6.4 and Moz-Bt 6 5

Addition of a solution of (benzotriazol-1 yl)carbonyl chloride in THF to a solution of *t*-butyl alcohol (2 eq) and pyridine (1 eq) in THF, dropwise, at -20 °C, after warming up to room temperature, afforded BOC Bt 6 4 as a colorless oil in 68% yield Similary addition of *p*-methoxybenzyl alcohol (1 eq) and pyridine (1 eq) gave crystalline Moz Bt 6 5 in 72% yield, after normal workup procedure and trituration with ether Both **6.4** and **6.5** are stable on storage for several weeks at room temperature without decomposition.

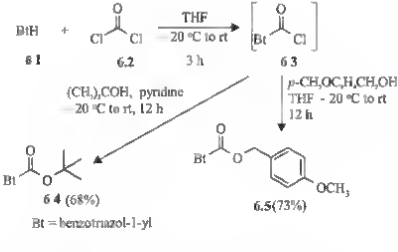
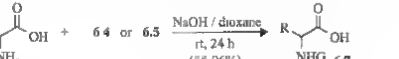


Figure 6 1

The reactivity of reagents **6.4** and **6.5** was tested with two amino acids phenylalanine (**6.6a**) and phenylglycine (**6.6b**) Both BOC-Bt **6.4** and Moz-Bt **6 5** reacted at 20 °C with amino acid **6 6a** or **6.6b** in dioxane in the presence of one equivalent of sodium hydroxide for 24 h to yield the *N*-protected amino acids **6.7** in satisfactory yields (figure 12) The separation of **6 7** was relatively simple. The only byproduct, benzotriazole (**6.1**), was extracted into organic solution after reaction, and the sodium salt of **6.7** was isolated by acidification of aqueous solution, followed by extraction with ether The pure product was finally obtained by recrystallization.



6 6a R = Ph
6 6b R = PhCH2

6 7a R = Ph, G = BOC
6.7b R = PhCH2, G = BOC
6.7c R = Ph, G = Moz
6.7d R = PhCH2, G = Moz

Figure 6.2

In conclusion, the results presented in this chapter have disclosed a convenient synthesis of two stable reagents, 1-(*t*-butoxycarbonyl)benzotriazole (**6.4**) and 1-(*p*- methoxybenzyloxycarbonyl)-benzotriazole (**6.5**) which were sufficiently reactive toward phenylalanine (**6.6a**) and phenylglycine (**6.6b**) to afford contaminant free *N*-protected amino acids Therefore, both reagents should be suitable for the preparation of other *N*-protected amino acids The advantage of these reagents lies in the good leaving ability of the benzotriazolyl moiety, which is readily displaced by the amino group The benzotriazole group displaced is easy to get rid of during the workup

6.3 Experimental

Melting points were determined on a Bristoline hot-stage microscope and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a 300 and 75 MHz spectrometer respectively Elemental analyses were carried out within the Department. The optical rotations were measured using Perkin Elmer 241 Polarimeter Column chromatography was conducted over silica gel (200-425 mesh, Kodak Co)

General Procedure for the Preparation of 1-(t-Butoxycarbonyl)benzotriazole (6.4) and 1-(*p*-Methoxybenzyloxycarbonyl)benzotriazole (6.5)

To a solution of phosgene (**6.2**) (100 mL, 20% in toluene) was added dropwise a solution of benzotriazole (**6.1**) (5 95 g, 50 mmol) in THF (50 mL) under nitrogen at -20 °C for 1 hour The reaction mixture was allowed to warm to room temperature

and stirred for another 2 hours. The solvents and excess phosgene were removed using rotary evaporation under reduced pressure in a fume hood to give (benzotriazol -1-yl)carbonyl chloride **(6.3)** in almost quantitative yield (based on ^{1}H NMR)

The above (benzotriazole-1-yl)carbonyl chloride **(6.3)** was dissolved in THF (40 mL) and the resulting solution was added dropwise to a solution of an appropriate alcohol, [*t*-butyl alcohol (2 equivaleats) (7 41 g, 100 mmol) or *p*-methoxybenzyl alcohol (1 equivalent) (6 91 g, 50 mmol)], and pyridine (1 equivalent) (3 96 g, 50 mmol) in THF (30 mL) under nitrogen at -20 °C The reaction mixture was allowed to warm to room temperature and stirred overnight. The solid was filtered off, and the filtrate washed with saturated sodium bicarbonate (3 x 50 mL) and water (3 x 50 mL), and dried ($MgSO_4$) Removal of solvent *in vacuo* gave the corresponding oily product **6.4** or 5 Compound 6 4 thus obtained was in good purity (7.45 g, 68% yield) and it was not necessary to purify further The analytical sample of BDC-Bt **6.4** was purified by short column chromatography using hexane/EtOAc (3 1) as the eluent. The white crystalline solid **6.5** was obtained (10 35 g, 73%) by trituration of crude oil with diethyl ether

1-(*t*-Botoxycarbooyl)beozotriazole (6 4) ^{1}H NMR ($CDCl_3$) δ 8 11 (d, J = 8 3 Hz, 1H), 8 05 (d, J = 8 3 Hz, 1H), 7 63 (t, J = 7 9 Hz, 1H), 7.48 (t, J = 7.4 Hz 1H) 1 82 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 146 8, 145 4, 131 2, 129 4, 125 1, 119 7, 113 1, 86.6, 27 6 HRMS (FAB) $C_{11}H_{13}N_3O_2$ (M^+) requires 219 1008 Found 219.1006

1-(*p*-Methoxybenzyloxycarbonyl)benzotriazole (6.5) White solid, mp 70-72 °C ^{1}H NMR ($CDCl_3$) δ 8 13 (d, J = 8 3 Hz, 1H), 8 09 (d, J = 8 3 Hz, 1H), 7 64 (t, J = 7.2

Hz, 1H), 7 53 (d, J = 8 8 Hz, 2H), 7 46-7 54 (m, 1H), 6 96 (d, J = 8 8 Hz, 2H), 5.59 (s, 2H) 3 84 (s, 3H), ^{13}C NMR ($CDCl_3$) δ 160 4, 148 9, 145 9, 131 8, 130 9, 130 1 126 1, 125 7, 120 4, 114 2, 113 5, 70 4, 55.3 Anal Calcd. for $C_{15}H_{13}N_3O_3$ C 63 60, H 4 63, N 14 83 Found C 63.39, H 4 54, N 14 83

General Procedure for the Protection of Amino Acids with BOC-Bt 6.4 and Moz-Bt 6.5

To a mixture of an amino acid (L-phenylglycine or L-phenylalanine) (5 mmol) and NaOH (0 20 g, 5 mmol) was added a 1 1 mixture of dioxane / water (20 mL) The reaction mixture was stirred until all solids had dissolved It was then cooled to 0 °C using an ice bath A solution of BOC-Bt 6.4 or Moz-Bt 6 5 (5 mmol) in 10 mL of dioxane was added dropwise. The reaction mixture was stirred for 24 h at room temperature The dioxane was evaporated off, and the residue diluted with water (30 mL) and extracted with ethyl acetate (3 X 30 mL) The aqueous layer was acidified with 1M H_2SO_4 to pH 2, and extracted with diethyl ether (3 X 50 mL) The combined organic layer was washed with water (3 X 50 mL) and dried over $MgSO_4$ Evaporation of the solvent gave the product in high purity The analytical samples were purified by recrystallization from ether/hexane

***N*-*t*-Butoxycarbonyl-L-pheonylglycine (6.7a)** white solid, 88% yield mp 110-112 °C $[\alpha]_D^{20}$ + 0.2° (c = 1 5 ethanol) ^{1}H NMR ($CDCl_3$) δ 12.50 (brs, 1H), 7 51 (brs, 1H), 7 29-7 43 (m, 5H), 5 13 (d, J = 8 1 Hz, 1H), 1 40 (s, 9H), ^{13}C NMR ($CDCl_3$) δ 172.2, 155 1, 137.4, 128 3, 127 7, 127 6, 78 3 57 6, 28 1 Anal Calcd for $C_{13}H_{17}N_1O_4$ C 62.14, H 6.82, N 5 57 Found C 61 77, H 7 16, N 5 70

***N*-*t*-Butoxycarbonyl-L-phenylalaine (6.7b)** white solid, 95% yield. mp 80-82 °C, lit mp 84-86 °C [77BCJ718], $[\alpha]_D^{26}$ + 20.3° (c = 1.5, ethanol), lit $[\alpha]_D^{26}$ +24.8° (c = 1.5, ethanol) ^{1}H NMR ($CDCl_3$) δ 12.50 (brs, 1H), 7.22-7.33 (m, 5H), 7.05 (d, *J* = 7.9 Hz, 1H), 4.10-4.18 (m, 1H) 3.05 (dd, *J*=13.5 and 4.2 Hz, 1H), 2.87 (dd, *J* = 13.5 and 3.4 Hz, 1H), 1.30 (s, 9H), ^{13}C NMR ($CDCl_3$) δ 173.5, 155.4, 138.0 129.0, 128.0, 126.2, 78.0, 55.1, 36.5, 28.1

***N*-*p*-Methoxybenzyloxycarbonyl-L-phenylglycine (6.7c)** white solid, 95% yield. mp 120-121 °C $[\alpha]_D^{26}$ + 117.7° (c = 1.5, ethanol). ^{1}H NMR ($CDCl_3$) δ 13.00 (brs, 1H), 8.01 (d, *J* = 7.4 Hz, 1H), 7.31-7.44 (m, 7H), 6.93 (d, *J* = 8.5 Hz, 2H), 5.19 (d, *J* = 8.0 Hz, 1H), 5.00 (s, 2H), 3.76 (s, 3H), ^{13}C NMR ($CDCl_3$): δ 172.0, 159.0, 155.9, 137.1, 129.7, 128.7, 128.3, 127.8, 127.7, 113.7, 65.4, 58.0, 55.1 Anal. Calcd for $C_{17}H_{17}N_1O_5$. C 64.74, H 5.44, N 4.44. Found: C 64.75, H 5.54, N 4.40

***N*-*p*-Methoxybenzyloxycarbonyl-L-phenylalaine (6.7d)** white solid, 96% yield. mp 84-85 °C, lit. mp 83-85 °C [62CB1] $[\alpha]_D^{25.1}$ + 7.6° (c = 1.5, ethanol) lit $[\alpha]_D^{20}$ +5.7° (c = 2.37, acetic acid) ^{1}H NMR ($CDCl_3$) δ 12.91 (brs, 1H), 7.56 (d, *J* = 8.0 Hz, 1H), 7.23-7.28 (m, 7H), 6.91 (d, *J* = 8.3 Hz, 2H), 4.93 (s, 2H), 4.24 (brs, 1H), 3.76 (s, 3H), 3.11 (dd, *J* = 13.9 and 3.9 Hz, 1H), 2.88 (dd, *J* = 13.9 and 3.3 Hz, 1H), ^{13}C NMR ($CDCl_3$) δ 173.3, 159.0, 156.1, 137.9, 129.5, 129.1, 128.9, 128.2, 126.4, 113.7, 65.2, 55.5, 55.1, 36.6

CHAPTER VII
REGIOSELECTIVITY OF REACTIONS OF ALLYLIC BENZOTRIAZOLE WITH ALDEHYDES AND KETONES IN THE PRESENCE OF LITHIUM

7.1 Introduction

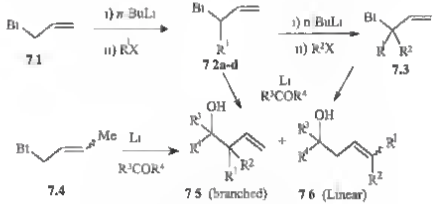
Allylmetals are important reagents in organic synthesis, particularly in their reactions with carbonyl compounds, which can be viewed as a complimentary method to Aldol reactions [93CR2207]. Allyllithium is one of the most useful allylmetals, however it has been reported to possess poor regioselectivity [91MI1, 70BCF1077, 72JOM49, 73JOC326, 74HCA496, 91MI1, 94T7857]. Therefore other metals, such as chromium [77JA3179, 82BCJ561] and titanium [83TL2865], are always used to achieve regio- and stereo-selectivity; unfortunately these reactions are quite limited due to the limited availability of starting materials. Cohen and co-workers developed a general and versatile method for generating allyllithiums from the reductive lithiation of phenyl thioethers [89ACR152]. Again, they found that the formed allyllithiums have low regioselectivity [86T2803], and transmetallation with titanium or cerium was required to achieve high regioselectivity [86T2803, 87JA4710].

More recently, it was demonstrated that allylbenzotriazoles can be transformed into the corresponding allyllithiums by reductive cleavage of a C-N bond [97JOC4116]. Considering that allylic benzotriazole undergoes alkylation exclusively at the position α to the benzotriazole group [97CR1p], various alkyl

groups can be introduced at the α-position followed by reductive cleavage of the benzotriazolyl group to give various substituted allylithium reagents which otherwise may not be readily available. This chapter reports that high regioselectivity is valid for the reaction of most carbonyl compounds with various α-substituted allyllithiums.

7.2 Results and Discussion

The reactions of allylbenzotriazole **7.1** with *n*-BuLi followed by the appropriate alkyl halide gave the α substituted allylbenzotriazoles **7.2a-d** in good yields (figure 7.1) and no further purification was needed. For compound **7.2b** the benzotriazol-1-yl isomer was isolated by column chromatography in 74% yield.



7.2a R^1 = Bu (94 %)
7.2b R^1 = Me (87 %)
7.2c R^1 = n-C_6H_{13} (90 %)
7.2d R^1 = Et (82 %)
7.3a R^1 = Et, R^2 = Me (68 %)
7.3b R^1 = Et, R^2 = n-C_6H_{13} (72 %)

Figure 7.1

The reaction of compound **7.2a** with an excess of lithium in the presence of cyclohexanone or 3-pentanone in THF (under Barbier-type reaction conditions) at -78 °C gave, after hydrolysis with water at -78 °C, branched products **7.5** (α-attack) in very high yields. A trace of the linear product (γ-attack) was detected by ^{1}H NMR, but could not be separated from the branched product by column chromatography. The reaction of **7.2b** or **7.2b** with 3-dodecanone gave predominantly the branched product, with only a trace of the linear product. When **2c-d** were reacted with aldehydes the major product obtained was again the branched product and a very small amount of the γ-attack product **7.6** was detected by GC. Similar regioselectivity was reported for substituted allylic halides using transition metals such as chromium and manganese [77JA3179,95SC33]. The α-attack product **7.5** was formed as a mixture of two diastereomers which were identified as threo and erythro, based on the difference in the coupling constant of the methine proton adjacent to the hydroxy group (figure 7.2). The higher coupling constant (7.5 Hz) corresponds to the threo isomer, as reported by Kimura and co-workers [81TL1037], while the smaller coupling constant (6.6 Hz), corresponds to the erythro isomer. The two diastereomers were formed in a 3.2 ratio, as shown by ^{1}H NMR, with the threo isomer being the major product.

N-(γ-Methylallyl)benzotriazole **7.4** (an isomer of **7.2b**) was prepared from crotyl bromide and its regioselectivity compared with **7.2b**. As shown in Table 7.1, the reactions of **7.4** with benzaldehyde, nonaldehyde and dodecanone gave the same products with a similar regioselectivity as for **7.2b**.

Table 7 1 Reaction of substituted allylbenzotriazoles **7.2-3** with carbonyl compounds

7.5/ 7 6	R^1	R^2	R^3	R^4	Total GC Yield % (Isolated)	Ratio of **7 5/7 6**
a	Bu	H	Et	Et	99 (75)	>99
b	Bu	H		-$(CH_2)_5$-	98 (78)	89 / 9
c	Me	H	CH_3CH_2-	-$(CH_2)_6CH_3$	79 (80)	94 / 6
d	Me	H	Ph	H	94 (87)	85 / 15
e	Me	H	$CH_3(CH_2)_7$-	H	99 (95)	94 / 6
f	*n*-C_6H_{13}	H	CH_3CH_2	-$(CH_2)_6CH_3$	100 (89)	97 / 3
g	*n*-C_6H_{13}	H	Ph	H	98 (88)	96 5
h	*n*-C_6H_{13}	H	$PhCH_2CH_2$-	H	95 (76)	88 / 12
i	*n*-C_6H_{13}	H	$(CH_3)_2C$	H	99 (74)	84 /16
j	*n*-C_6H_{13}	H	$(CH_3)_2CH$-	H	94 (77)	82 / 18
k	Et	H	$C_6H_5CHC_2H_5$-	H	82 (73)	85 / 15
l	H	Me	CH_3CH_2-	-$(CH_2)_6CH_3$	86 (70)	94 / 4
m	H	Me	$CH_3(CH_2)_7$-	H	98 (84)	95 5 / 4 5
n	H	Me	Ph	H	98 (86)	>99
o	H	Me	Ph	CH_3	93 (81)	94 / 6
p	H	Me	$Ph(CH_2)_2$-	H	99 (78)	89 /11
q	H	Me	C_5H_{11}-	H	99 (90)	>99
r	Et	Me	Et	Et	(87)	**7.5** only
s	Et	Bu	Et	Et	(99)	89/10

The reaction with benzaldehyde clearly showed a mixture of three and erythro isomers, with the major isomer (59%) being the three These results suggest that both

starting materials (**7.2b** and **7.4**) go through a common intermediate **7.7** (figure 7.2) and the addition to electrophiles occurs at the more substituted carbon, giving mainly the terminal alkene. All these results are summarized in Table 7.1.

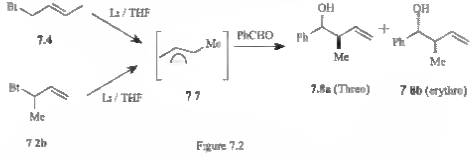


Figure 7.2

Comparing all the results in Table 7.1, better regioselectivity was generally observed with the ketones than with the aldehydes. The regioselativity decreased slightly with an increase in branching of the aldehydes (entry 5-7 and 11), probably due to steric effects. The stereoselectivity remained low, as previously reported for allyllithiums [91MI1, 89ACR152].

In conclusion, these results show the first example of allyllithiums generated from substituted allylbenzotriazoles in the presence of lithium which reacted with ketones and aldehydes with high regioselectivity. This methodology has three major advantages over other reported methods using lithium: (i) high regioselectivity can be achieved without transmetallation or use of a catalyst, (ii) easy accessibility to various α-substituted allyllithiums that otherwise are not readily obtained, and (iii) the main byproduct, benzotriazole, can be washed away by a basic aqueous solution, which avoids the use of acid in the work-up.

7.3 Experimental

Melting points were determined on a Thomas-Hoover capillary melting point apparatus or on a Kofler hot plate microscope and are uncorrected. ^{1}H and ^{13}C NMR spectra were obtained on either a Varian VXR 300 MHz or a Gemini 300 MHz spectrometer with tetramethylsilane as the internal standard. Coupling constants are given in Hz. Low resolution mass spectra were recorded on a Hewlett-Packard 5890 gas chromatograph, equipped with a Hewlett Packard 5972 mass selective detector. Compounds **7.1, 7.2a-d** were prepared according to literature method [92LA843] and compound **7.3** and **7.4** were prepared using the same procedure.

General procedure for the reactions of compounds 7.2a-d, 7.3a-b and 7.4 with lithium and electrophiles

Lithium (25 mmol, 30% dispersion in mineral oil) was washed twice with THF under argon. THF (5 mL) was added and the suspension was cooled to -78 °C. A solution of the appropriate allylbenzotriazole (5 mmol) and electrophile (5 mmol) in THF (25 mL) was added to the lithium suspension over 1 hour and kept another 1-4 h before being quenched with water (15 mL) at the same temperature. After usual work-up, the crude product was purified by flash column chromatography on silica gel.

3-Ethyl-4-allyl-octan-3-ol (5a) Oil, ^{1}H NMR ($CDCl_3$) δ 5.71-5.59 (m, 1 H), 5.14 (dd, J = 2.2, 10.2 Hz, 1 H), 5.05 (dd, J = 1.9, 17.1 Hz, 1 H), 2.12-2.04 (m, 1 H), 1.59-1.06 (m, 11 H), 0.95-0.78 (m, 9 H), ^{13}C NMR ($CDCl_3$) δ 139.2, 117.5, 75.2, 51.5, 30.3, 28.5, 28.4, 27.7, 22.7, 14.0, 7.5, 7.3.

1-(1-Hepten-3-yl)-1-cyclohexanol (5b): Oil, ^{1}H NMR ($CDCl_3$) δ 5 67-5 58 (m, 1H), 5 13 (dd, J = 2 2, 10 23 Hz, 1 H), 5 03 (dd, J = 1 9, 17 1 Hz, 1 H), 1 93-1 85 (m, 1 H), 1 62-1 05 (m, 17 H), 0 88 (t, J = 6 9 Hz, 3 H), ^{13}C NMR ($CDCl_3$): δ 139 2, 117 5, 72 4, 55 6, 34 8, 30 2, 27 6, 25 9, 22 7, 22.2, 22 1, 21 8,14 0 Anal Calcd for $C_{13}H_{24}O$: C 79 53, H 12.32 Found C 79 46, H 12 32

3-(1-Methylallyl)dodecan-3-ol (5c) Oil, ^{1}H NMR ($CDCl_3$) δ 5 95-5 83 (m, 1 H), 5 08 (d, J = 11 5Hz, 1 H), 5 07 (d, J = 15 6Hz, 1 H), 2.44-2 32 (m, 2 H), 1 60-1 44 (m, 2 H), 1 40-1 29 (m, 16 H), 1 02 (d, J = 8 9 Hz, 3 H), 0 90-0 77 (m 8 H), ^{13}C NMR ($CDCl_3$) δ 140 6, 115.5, 75 2, 44 8, 36.2, 31.9, 30 4, 29 7, 29 4, 28 5, 22 7, 14.2, 14.0, 7 6, 7.5 Anal. Calcd for $C_{16}H_{32}O$ C 79 93, H 13 42. Found C 79 85, H 13 45

3-(1-hexylallyl)decan-3-ol (5f) Oil, ^{1}H NMR ($CDCl_3$) δ 5 69 5 60 (m, 1 H), 5 18-5 03 (m, 2 H), 2 47-2.39 (m, 2 H), 2 14-2 06 (m 1 H) 1 59 1.29 (m, 28 H), 1 07 (t, J = 7 2Hz, 3 H), 0 00-0 78 (m 6 H), ^{13}C NMR ($CDCl_3$) δ 139 2, 117 6, 75 2, 52.0 (51 8), 42 4, 36 4 (36 2) 35 8 31 9 (31 8) 30 4, 29 6 (29 5) 29 4 (29.3), 29 2 (29 0) 28 1 (28 0) 24 0 (23 1), 23 0 (22 6), 14 0, 7 8 (7 5)

1-Phenyl-2-Hexyl-3-butene-1-ol (5g) Oil, H NMR ($CDCl_3$) δ 7.32-7 21 (m, 5 H), 5 67-5 43 (m, 1 H), 5 24-4 94 (m, 2 H) 4 58 (d J =5 5Hz, 1 H), 4 37 (d, J = 7 7Hz, 1 H), 2 41 2 20 (m, 2 H), 1.25 1 18 (m, 10 H) 0 88-0 81 (m, 3 H), ^{13}C NMR ($CDCl_3$) δ 142 6 139 4, 138 7, 128.2 128.1 128 0, 127 9 127 5, 127 2, 126 9, 126 7, 117 1, 77 4, 78 6, 52 6, 51 4, 31 8, 31 7, 30 4, 29 6, 29.3 29 1, 27 1, 22 6, 22.5, 14 0.

1-Phenyl-4-allyl-decan-3-ol (5h) Oil, ^{1}H NMR ($CDCl_3$) δ 7.31-7 09 (m, 10 H), 5 66-5 51 (m, 1 H), 5 20-5 04 (m, 2 H) 3 58-3 45 (m, 1 H), 2.93-2.58 (m, 4 H),

1 24 -1 19 (m, 14 H), 0 88-0 01 (m, 3 H), Anal. Calcd. for $C_{18}H_{34}O$ C 83 02, H 10 84 Found. C 82.93, H 10 30

1,1-dimethyl-4-vinyl-decan-3-ol (5i), Oil, ^1H NMR ($CDCl_3$) δ 5.91-5 66 (m, 1 H), 5 11-4 92 (m, 2 H), 3 40-3.20 (br, s, 1 H), 2 32-1 93 (m, 2 H), 1 58-1 14 (br, s, 10 H), 1 00-0 65 (m, 12 H), ^{13}C NMR ($CDCl_3$) δ 142.6 (139 1), 134.5 (133 3), 127 4 (126 7), 116 1 (114.1), 81 9 (81 7), 79 1 (78 2) 46 7 (45 4), 35 8 (35 3), 34 4, 31 8 (31 7), 29 8 (29 6), 28 9 (28 8), 27 3 (27 2), 26 8 (26 7), 25 8, 22 6 (22 5), 14 0 Anal Calcd. for $C_{14}H_{28}O$ C 79 18, H 13 29 Found C 78 75, H 13 05

1-Cyclohaxyl-2-allyl-octan-1-ol (5j): Oil, ^1H NMR ($CDCl_3$) δ 5 71 5.53 (m, 1 H), 5 18-5 00 (m 2 H), 3.21 3.15 (m, 1 H) 2 34-2 00 (m, 2 H), 1 83-1 10 (m, 20 H), 1 00-0 87 (m, 3 H) ^{13}C NMR ($CDCl_3$) δ 140 3 (138 9), 134 8 (133 4), 126.3 (125 6), 117.2 (115 7), 78 8 (77 6), 75 6 (74 9), 47.3 (46 6), 43 1 (43 0), 40 5 (40 4), 37.6, 32 7 (32.2), 31 8 (31 7), 29.7 (29 6), 29 4 (29 3), 29.2 (29 1), 29 0 (28 9), 28 8 (28 2), 27 6 (27 4), 27 2 (27 1), 26 5 (26 4), 26 3 (26 2), 22 6 14 0

3,5-Diethyl-1-nonen-4-ol (5k) Oil ^1H NMR ($CDCl_3$) δ 5 72 5 60 (m, 1 H), 5.23 -5 11 (m, 2 H), 3.41 (br, s, 1 H), 2 12 2.05 (m, 1 H), 1 57-1 10 (m, 13 H) 0 99-0 78 (m, 9 H)

3-Ethyl-4-methyl-4-allyl-hexan-3-ol (5l) Oil ^1H NMR ($CDCl_3$) δ 5 86 (dd, *J*=10 8, 17 6Hz, 1 H), 5 20 (d, *J* = 9 6Hz, 1 H), 5 03 (d, *J* = 17 7Hz, 1 H), 1 64-1 43 (m, 6 H), 0 99-0 88 (m, 9 H), 0 75 (t, *J* = 7 4Hz, 3 H), ^{13}C NMR ($CDCl_3$) δ 144 1, 115 0, 77 1, 48 9, 27.3, 27 1, 16 3 9.2, 8.9 Anal Calcd for $C_{11}H_{22}O$ C 77 58 H 13 02 Found C 77 31, H 13.56

3-Ethyl-4-ethyl-4-allyl-docan-3-ol (5m) Oil ^{1}H NMR ($CDCl_3$) δ 5.80 (dd, J = 11.2, 17.7Hz, 1 H), 5.17 (d, J = 11Hz, 1 H), 4.98 (d, J = 17.9Hz, 1 H), 1.67-1.59 (m, 8 H), 1.29-1.26 (m, 10 H), 0.94-0.85 (m, 12 H), ^{13}C NMR ($CDCl_3$) δ 144.2, 114.6, 78.2, 50.5, 31.9, 31.5, 30.8, 28.1, 28.0, 25.0, 24.0, 22.8, 14.1, 9.7, 9.3 Anal. Calcd. for $C_{16}H_{32}O$: C, 79.93; H, 13.42. Found: C, 79.91; H, 13.39.

3-Methyl-1-dodecene-4-ol (5o), Oil, ^{1}H NMR ($CDCl_3$) δ 5.83-5.70 (m, 1 H), 5.12-5.51 (m, 2 H), 3.48-3.36 (m, 1 H), 2.28-2.17 (m,1 H), 1.70-1.55 (m, 2 H), 1.48-1.28 (m, 13 H), 1.07-0.97 (m, 3 H), 0.90-0.86 (m, 3 H), ^{13}C NMR ($CDCl_3$) δ 141.2 (140.4), 128 (127.2), 116.0 (115.0), 74.7 (73.0), 44.0 (43.9), 43.4 40.7, 36.8, 34.3 (34.1), 31.9 (31.8), 29.7 (29.6), 29.3 (29.2), 26.0 (25.8), 22.6, 16.2, 14.0. Anal. Calcd. for $C_{13}H_{26}O$: C, 78.72, H, 13.21. Found: C, 78.67, H, 13.57.

1-Pheuyl-2-methyl-3-buteue-1-ol (5p)• Oil, ^{1}H NMR ($CDCl_3$) δ (Mixture of two diastereomers, erythro / threo, 65:35) 7.30-7.21 (m, 5 H), 5.81-5.66 (m, 1 H), 5.18-4.98 (m, 2 H), 4.53 (d, J = 5.4 Hz, CHOH, erythro, 1 H), 4.31 (d, J = 7.5 Hz, CHOH, threo, 1 H), 2.57-2.25 (m, 2 H), 0.99 (d, J = 6.6 Hz, 3 H, erythro), 0.85 (d, J = 6.7 Hz, 3 H, threo), ^{13}C NMR ($CDCl_3$) δ (Mixture of two diastereomers, erythro / threo), 142.6 (142.4), 140.5 (140.3), 128.2 (128.), 127.9 (127.5), 127.2, 126.7 (126.4), 115.5 (115.3), 77.8 (77.2), 45.0 (44.5), 16.4 (14.1).

1-Pheuyl-1,2-dimethyl-3-buteo-1-ol (5q) Oil, ^{1}H NMR ($CDCl_3$) δ 7.41 (t, J = 7.3Hz, 2 H), 7.32 (t, J = 7.5Hz, 2 H), 7.24 (d, J = 5.7Hz, 1 H), 5.79-5.65 (m, 1 H), 5.12-5.06 (m, 2 H), 2.58-2.51 (m, 1 H), 2.17 (s, 1 H), 1.52 (s, 3 H), 0.91 (dd, J = 6.9, 28.6Hz, 3 H), ^{13}C NMR ($CDCl_3$) δ 147.0, 139.9, 127.8, 126.5, 126.3, 125.4, 125.2,

116.4, 116.1, 75.6, 65.7, 48.9, 48.7, 28.4, 25.9, 15.2, 14.7, 14.1. Anal. Calcd. for $C_{12}H_{16}O$: C, 81.77; H, 9.15. Found: C, 81.81; H, 9.17.

1-Phenyl-4-ethyl-5-hexen-3-ol (5r). Oil. ^{1}H NMR ($CDCl_3$): δ 7.32-7.17 (m, 5 H), 5.84-5.70 (*m*, 1 H), 5.15-5.07 (m, 2 H), 3.52-3.40 (*m*, 1 H), 2.92-2.260 (*m*, 3 H), 2.33-2.21 (m, 1 H), 1.89-1.63 (*m*, 4 H), 1.04 (d, J = 6.9Hz, 3 H); ^{13}C NMR ($CDCl_3$): δ 142.2, 140.8, 140.1, 128.4, 128.3, 126.9, 125.7, 116.3, 115.3, 74.0, 73.9, 70.2, 44.2, 43.7, 40.8, 38.4, 36.1, 35.8, 32.4, 32.1, 32.0, 16.2, 14.3. Anal. Calcd. for $C_{13}H_{18}O$: C, 82.06; H, 9.53. Found: C, 81.67; H, 9.54.

7-methyl-8-nonen-6-ol (5s). Oil. ^{1}H NMR ($CDCl_3$): δ 5.86-5.71 (m, 1 H), 5.12-5.04 (m, 2 H), 3.47-3.40 (m, 1 H), 2.25-2.16 (m, 1 H), 1.89-1.31 (m, 10 H), 1.05-1.01 (m, 2 H), 0.97-0.88 (*m*,3 H).

CHAPTER VIII
SUMMARY AND CONCLUSION

Various heterocycles have been synthesized and other organic transformations have been achieved by applying the properties of benzotriazole. 2-[(Benzotriazol-1-yl)methyl]-pyrroles and -indoles were prepared and used as building blocks in the synthesis of a variety of fused five and six membered heterocycles. This provides a general route to the skeleton of pyrrolizidine alkaloids which are found in compounds with biological activity, such as mitomycins.

The side chain of 2-[(benzotriazol-1-yl)methyl]furan was readily elaborated by lithiation, alkylation and subsequent intramolecular cyclizations via [3+2] annulations to give benzo[*b*]furans derivatives substituted at various positions. Such polysubstituted benzo[b]furan derivatives are not readily available by known methods.

The usefulness of benzotriazole methodology was further demonstrated in the synthesis of 1,2,3 triazoline and aziridine *via* 1,3-dipolar cycloaddition of azides bearing methylheterocycles.

Investigation of the addition reaction of immonium cations and benzotriazolyl anion to acetylenes showed that the addition follows a different mechanism than the addition to enamines or enol ethers, as demonstrated in chapter 5. The benzotriazolyl anion first undergoes a Michael addition followed by the addition of the immonium cation.

A new method of cleaving benzotriazole has been established by the reductive cleavage of benzotriazole in the presence of lithium, generating allyllithiums which were trapped regioselectively with aldehydes and ketones

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(1) References are listed in order of year of publication, alphabetical order of the journal abbreviation code and page number (2) The reference code is followed by the conventional literature citation complete with the name of the authors. (3) For journals that are published in separate parts, the letter or number is given (when necessary) in parentheses immediately after the journal code letters (4) Less common journals and books are assigned the code "MI" for miscellaneous.

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I certify that I have read this study and that in my opinion it conforms to acceptable standards of scholarly presentation and is fully adequate in scope and quality as a dissertation for the degree of Doctor of Philosophy

Alan R. Katritzky, Chair
Kenan Professor of Chemistry

I certify that I have read this study and that in my opinion it conforms to acceptable standards of scholarly presentation and is fully adequate, in scope and quality, as a dissertation for the degree of Doctor of Philosophy

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